

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CSPC PHARMACEUTICAL GROUP LIMITED,
CSPC OUYI PHARMACEUTICAL CO., LTD.,
AND CONJUPRO BIOTHERAPEUTICS, INC.,
Petitioners,

v.

IPSEN BIOPHARM LTD.,
Patent Owner.

Case No. IPR2025-00505
U.S. Patent No. 11,344,552

**DECLARATION OF JUNE A. MUNFORD, MILS,
IN SUPPORT OF PATENT OWNER'S RESPONSE TO PETITION FOR
INTER PARTES REVIEW OF U.S. PATENT NO. 11,344,552**

I, June Ann Munford, declare as follows:

I. INTRODUCTION

1. My name is June Ann Munford. I have been retained as an expert by Counsel for Ipsen Biopharm Ltd. (referred to herein as “Ipsen”).

2. I submit this declaration at the request of Ipsen in order to provide information regarding the authenticity and public availability of the publications cited in Ipsen’s Patent Owner Response and accompanying Declaration of Paul E. Oberstein.

3. I reserve the right to supplement or amend this declaration in response to any additional information that may be provided to me or that I come to learn after the date of this declaration.

4. I am being compensated for my time spent working on this matter at my normal consulting rate of \$200 per hour, plus reimbursement for any additional reasonable expenses. My compensation is not in any way tied to the content of this declaration or the outcome of this proceeding. I have no other interests in this proceeding or with any of the parties.

5. All of the materials that I considered are discussed explicitly in this declaration.

II. QUALIFICATIONS

1. I earned a Master of Library and Information Science (MLIS) from the University of Wisconsin-Milwaukee in 2009. I have over ten years of experience in the library/information science field. Beginning in 2004, I have served in various positions in the public library sector including Assistant Librarian, Youth Services Librarian and Library Director. I have attached my Curriculum Vitae as Appendix CV.

2. During my career in the library profession, I have been responsible for materials acquisition for multiple libraries. In that position, I have cataloged, purchased and processed incoming library works. That includes purchasing materials directly from vendors, recording publishing data from the material in question, creating detailed material records for library catalogs and physically preparing that material for circulation. In addition to my experience in acquisitions, I was also responsible for analyzing large collections of library materials, tailoring library records for optimal catalog search performance and creating lending agreements between libraries during my time as a Library Director.

3. I am fully familiar with the catalog record creation process in the library sector. In preparing a material for public availability, a library catalog record describing that material would be created. These records are typically written in Machine Readable Catalog (herein referred to as “MARC”) code and contain

information such as a physical description of the material, metadata from the material's publisher, and date of library acquisition. In particular, the 008 field of the MARC record is reserved for denoting the date of creation of the library record itself. As this typically occurs during the process of preparing materials for public access, it is my experience that an item's MARC record indicates the date of an item's public availability.

4. Typically, in creating a MARC record, a librarian would gather various bits of metadata such as book title, publisher and subject headings among others and assign each value to a relevant numerical field. For example, a book's physical description is tracked in field 300 while title/attribution is tracked in field 245. The 008 field of the MARC record is reserved for denoting the creation of the library record itself. As this is the only date reflecting the inclusion of said materials within the library's collection, it is my experience that an item's 008 field accurately indicates the date of an item's public availability.

5. I am familiar with the Internet Archive, a digital library accessible to the general public. Among other services that the Internet Archive makes available to the general public is the Wayback Machine, an online archive of the web. The Internet Archive's Wayback Machine service archives webpages as of a certain capture date to track changes in the web over time. The Internet Archive has been in operation as a nonprofit library since 1996 and has hosted the Wayback Machine

service since its inception in 2001. During my time as a librarian, I frequently used the Internet Archive's Wayback Machine for research and instruction purposes. This includes teaching instructional classes on using the Wayback Machine to library patrons and using the Wayback Machine to research reference inquiries that require hard-to-find online resources. I consider the Internet Archive's recordskeeping to be as rigorous and detailed as other formal library recordskeeping practices such as MARC records, OCLC records and Dublin Core.

III. PUBLICATIONS

A. Marsh (Ex. 2004)

1. I have reviewed Exhibit 2004, "Pancreatic Cancer and FOLFIRINOX: A New Era and New Questions" by Robert De W. Marsh, et al. as published in Cancer Medicine February 19, 2015.

2. Attached hereto as Appendix MARSH01 is a true and correct copy of the MARC record for Cancer Medicine as held by the Penn State University Library. I secured this record myself from the library's public catalog. The MARC record contained within Appendix MARSH01 accurately describes the title, publisher and ISSN number of Cancer Medicine. The Showing Results field present on page 3 of this record indicates the library's collection includes the February 19, 2015 issue of Cancer Medicine containing "Pancreatic Cancer and FOLFIRINOX: A New Era and New Questions."

3. Attached hereto as Appendix MARSH02 is a true and correct copy of “Pancreatic Cancer and FOLFIRINOX: A New Era and New Questions” as published in Cancer Medicine as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2004 to Appendix MARSH02, it is my determination that Exhibit 2004 is a true and correct copy of “Pancreatic Cancer and FOLFIRINOX: A New Era and New Questions” by Robert De W. Marsh, et al. as published in Cancer Medicine.

4. The 008 field of the MARC record in Appendix MARSH01 indicates the date of record creation. The 008 field of Appendix MARSH01 indicates the Penn State University Library first acquired Cancer Medicine as of June 6, 2012 and held the journal in perpetuity until the publication of “Pancreatic Cancer and FOLFIRINOX: A New Era and New Questions.” Considering this information, it is my determination that Cancer Medicine February 19, 2015 and therefore “Pancreatic Cancer and FOLFIRINOX: A New Era and New Questions” was made available to the public shortly after its initial publication as of February 19, 2015.

B. Rossi (Ex. 2006)

5. I have reviewed Exhibit 2006, “Therapeutic Options for the Management of Pancreatic Cancer” by Maria L. Rossi, et al. as published in World Journal of Gastroenterology August 2014.

6. Attached hereto as Appendix ROSSI01 is a true and correct copy of the MARC record for World Journal of Gastroenterology as held by the Penn State University Library. I secured this record myself from the library's public catalog. The MARC record contained within Appendix ROSSI01 accurately describes the title, publisher and ISSN number of World Journal of Gastroenterology. The Showing Results field present on page 3 of this record indicates the library's collection includes the August 2014 issue of World Journal of Gastroenterology containing "Therapeutic Options for the Management of Pancreatic Cancer."

7. Attached hereto as Appendix ROSSI02 is a true and correct copy of "Therapeutic Options for the Management of Pancreatic Cancer" as published in World Journal of Gastroenterology as held by the Penn State University Library. This PDF was secured from the library's collection. In comparing Exhibit 2006 to Appendix ROSSI02, it is my determination that Exhibit 2006 is a true and correct copy of "Therapeutic Options for the Management of Pancreatic Cancer" by Maria L. Rossi, et al. as published in World Journal of Gastroenterology.

8. The 008 field of the MARC record in Appendix ROSSI01 indicates the date of record creation. The 008 field of Appendix ROSSI01 indicates the Penn State University Library first acquired World Journal of Gastroenterology as of October 16, 2003 and held the journal in perpetuity until the publication of "Therapeutic Options for the Management of Pancreatic Cancer." Considering this

information, it is my determination that World Journal of Gastroenterology August 2014 and therefore “Therapeutic Options for the Management of Pancreatic Cancer” was made available to the public shortly after its initial publication in August 2014.

C. Valsecchi (Ex. 2007)

9. I have reviewed Exhibit 2007, “Recent Treatment Advances and Novel Therapies in Pancreas Cancer: A Review” by Matias E. Valsecchi, et al. as published in Journal of Gastrointestinal Cancer June 2014.

10. Attached hereto as Appendix VALSECCHI01 is a true and correct copy of the MARC record for Journal of Gastrointestinal Cancer as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix VALSECCHI01 accurately describes the title, publisher and ISSN number of Journal of Gastrointestinal Cancer. The Showing Results field present on page 3 of this record indicates the library’s collection includes the June 2014 issue of Journal of Gastrointestinal Cancer containing “Recent Treatment Advances and Novel Therapies in Pancreas Cancer: A Review.”

11. Attached hereto as Appendix VALSECCHI02 is a true and correct copy of “Recent Treatment Advances and Novel Therapies in Pancreas Cancer: A Review” as published in Journal of Gastrointestinal Cancer as held by the Penn State University Library. This PDF was secured from the library’s collection. In

comparing Exhibit 2007 to Appendix VALSECCHI02, it is my determination that Exhibit 2007 is a true and correct copy of “Recent Treatment Advances and Novel Therapies in Pancreas Cancer: A Review” by Matias E. Valsecchi, et al. as published in Journal of Gastrointestinal Cancer.

12. The 008 field of the MARC record in Appendix VALSECCHI01 indicates the date of record creation. The 008 field of Appendix VALSECCHI01 indicates the Penn State University Library first acquired Journal of Gastrointestinal Cancer as of March 13, 2008 and held the journal in perpetuity until the publication of “Recent Treatment Advances and Novel Therapies in Pancreas Cancer: A Review.” Considering this information, it is my determination that Journal of Gastrointestinal Cancer June 2014 and therefore “Recent Treatment Advances and Novel Therapies in Pancreas Cancer: A Review” was made available to the public shortly after its initial publication in June 2014.

D. BIO Study (Ex. 2008)

13. I have reviewed Exhibit 2008, a document entitled Clinical Development Success Rates 2006 - 2015.

14. Attached hereto as Appendix BIO01 is a screen capture of the Internet Archive Wayback Machine entry for <https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf>.

I secured these screen captures myself from <https://web.archive.org/web/20160701210803/https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf>. This record was captured as of July 1, 2016.

15. Appendix BIO01 is an Internet Archive capture of a file entitled Clinical Development Success Rates 2006 - 2015 as hosted on the Bio.org website. In comparing Appendix BIO01 to Exhibit 2008, it is my determination that Exhibit 2008 is a true and correct copy of Clinical Development Success Rates 2006 - 2015 as hosted on the Bio.org website. As the Internet Archive first captured this file as of July 1, 2016, it is my determination that Clinical Development Success Rates 2006 - 2015 was first made available to the public as of July 1, 2016 via the Internet Archive and likely earlier via the original Bio.org website.

E. Thota (Ex. 2009)

16. I have reviewed Exhibit 2009, “Preclinical Rationale for the Phase III Trials in Metastatic Pancreatic Cancer” by Ramya Thota, et al. as published in Pancreas February 2017.

17. Attached hereto as Appendix THOTA01 is a true and correct copy of the MARC record for Pancreas as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record

contained within Appendix THOTA01 accurately describes the title, publisher and ISSN number of Pancreas. The Showing Results field present on page 3 of this record indicates the library's collection includes the February 2017 issue of Pancreas containing "Preclinical Rationale for the Phase III Trials in Metastatic Pancreatic Cancer."

18. Attached hereto as Appendix THOTA02 is a true and correct copy of "Preclinical Rationale for the Phase III Trials in Metastatic Pancreatic Cancer" as published in Pancreas as held by the Penn State University Library. This PDF was secured from the library's collection. In comparing Exhibit 2009 to Appendix THOTA02, it is my determination that Exhibit 2009 is a true and correct copy of "Preclinical Rationale for the Phase III Trials in Metastatic Pancreatic Cancer" by Ramya Thota, et al. as published in Pancreas.

19. The 008 field of the MARC record in Appendix THOTA01 indicates the date of record creation. The 008 field of Appendix THOTA01 indicates the Penn State University Library first acquired Pancreas as of August 21, 2001 and held the journal in perpetuity until the publication of "Preclinical Rationale for the Phase III Trials in Metastatic Pancreatic Cancer." Considering this information, it is my determination that Pancreas February 2017 and therefore "Preclinical Rationale for the Phase III Trials in Metastatic Pancreatic Cancer" was made available to the public shortly after its initial publication in February 2017.

F. Ratain 2005 (Ex. 2010)

20. I have reviewed Exhibit 2010, “Phase II Oncology Trials: Let's Be Positive” by Mark J. Ratain as published in Clinical Cancer Research August 2005.

21. Attached hereto as Appendix RATAIN01 is a true and correct copy of the MARC record for Clinical Cancer Research as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix RATAIN01 accurately describes the title, publisher and ISSN number of Clinical Cancer Research. The Showing Results field present on page 3 of this record indicates the library's collection includes the August 2005 issue of Clinical Cancer Research containing “Phase II Oncology Trials: Let's Be Positive.”

22. Attached hereto as Appendix RATAIN02 is a true and correct copy of “Phase II Oncology Trials: Let's Be Positive” as published in Clinical Cancer Research as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2010 to Appendix RATAIN02, it is my determination that Exhibit 2010 is a true and correct copy of “Phase II Oncology Trials: Let's Be Positive” by Mark J. Ratain as published in Clinical Cancer Research.

23. The 008 field of the MARC record in Appendix RATAIN01 indicates the date of record creation. The 008 field of Appendix RATAIN01 indicates the

Penn State University Library first acquired Clinical Cancer Research as of January 29, 2001 and held the journal in perpetuity until the publication of “Phase II Oncology Trials: Let's Be Positive.” Considering this information, it is my determination that Clinical Cancer Research August 2005 and therefore “Phase II Oncology Trials: Let's Be Positive” was made available to the public shortly after its initial publication in August 2005.

G. De La Cruz (Ex. 2014)

24. I have reviewed Exhibit 2014, “Diagnosis and Management of Pancreatic Cancer” by Maria Syl D. De La Cruz, et al. as published in American Family Physicians April 15, 2014.

25. Attached hereto as Appendix DELACRUZ01 is a true and correct copy of the MARC record for American Family Physicians as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix DELACRUZ01 accurately describes the title, publisher and ISSN number of American Family Physicians. The Showing Results field present on page 3 of this record indicates the library's collection includes the April 15, 2014 issue of American Family Physicians containing “Diagnosis and Management of Pancreatic Cancer.”

26. Attached hereto as Appendix DELACRUZ02 is a true and correct copy of “Diagnosis and Management of Pancreatic Cancer” as published in American

Family Physicians as held by the Penn State University Library. This PDF was secured from the library's collection. In comparing Exhibit 2014 to Appendix DELACRUZ02, it is my determination that Exhibit 2014 is a true and correct copy of "Diagnosis and Management of Pancreatic Cancer" by Maria Syl D. De La Cruz, et al. as published in American Family Physicians.

27. The 008 field of the MARC record in Appendix DELACRUZ01 indicates the date of record creation. The 008 field of Appendix DELACRUZ01 indicates the Penn State University Library first acquired American Family Physicians as of October 11, 2000 and held the journal in perpetuity until the publication of "Diagnosis and Management of Pancreatic Cancer." Considering this information, it is my determination that American Family Physicians April 15, 2014 and therefore "Diagnosis and Management of Pancreatic Cancer" was made available to the public shortly after its initial publication as of April 15, 2014.

H. Schober (Ex. 2015)

28. I have reviewed Exhibit 2015, "New Advances in the Treatment of Metastatic Pancreatic Cancer" by Marvin Schober, et al. as published in Digestion October 2015.

29. Attached hereto as Appendix SCHOB01 is a true and correct copy of the MARC record for Digestion as held by the University of Toronto Library. I secured this record myself from the library's public catalog. The MARC record

contained within Appendix SCHOBER01 accurately describes the title, publisher and ISSN number of Digestion. The View Online field present on page 2 of this record indicates the library's collection includes the October 2015 issue of Digestion containing “New Advances in the Treatment of Metastatic Pancreatic Cancer.”

30. Attached hereto as Appendix SCHOBER02 is a true and correct copy of “New Advances in the Treatment of Metastatic Pancreatic Cancer” as published in Digestion as held by the University of Toronto Library. This PDF was secured from the library’s collection. In comparing Exhibit 2015 to Appendix SCHOBER02, it is my determination that Exhibit 2015 is a true and correct copy of “New Advances in the Treatment of Metastatic Pancreatic Cancer” by Marvin Schober, et al. as published in Digestion.

31. The 008 field of the MARC record in Appendix SCHOBER01 indicates the date of record creation. The 008 field of Appendix SCHOBER01 indicates the University of Toronto Library first acquired Digestion as of August 3, 2000 and held the journal in perpetuity until the publication of “New Advances in the Treatment of Metastatic Pancreatic Cancer.” Considering this information, it is my determination that Digestion October 2015 and therefore “New Advances in the Treatment of Metastatic Pancreatic Cancer” was made available to the public shortly after its initial publication in October 2015.

I. Dorland's Dictionary (Ex. 2017)

32. I have reviewed Exhibit 2017, Dorland's Illustrated Medical Dictionary by Elsevier Health Sciences.

33. Attached hereto as Appendix DORLAND01 is a true and correct copy of the MARC record for Dorland's Illustrated Medical Dictionary as held by the Penn State University Library. I secured this record myself from the library's public catalog. The MARC record contained within Appendix DORLAND01 accurately describes the title, author, publisher, and ISBN number of Dorland's Illustrated Medical Dictionary.

34. Attached hereto as Appendix DORLAND02 is a true and correct copy of Dorland's Illustrated Medical Dictionary as held by the Penn State University Library. This PDF was secured from the library's collection. In comparing Exhibit 2017 to Appendix DORLAND02, it is my determination that Exhibit 2017 is a true and correct copy of Dorland's Illustrated Medical Dictionary by Elsevier Health Sciences.

35. The 008 field of the MARC record in Appendix DORLAND01 indicates the date of record creation. The 008 field of Appendix DORLAND01 indicates the Penn State University Library first acquired Dorland's Illustrated Medical Dictionary as of October 3, 2013. Considering this information, it is my

determination that Dorland's Illustrated Medical Dictionary was made available to the public shortly after its initial acquisition as of October 3, 2013.

J. Stedman's Dictionary (Ex. 2018)

36. I have reviewed Exhibit 2018, Stedman's Medical Dictionary for the Health Professions and Nursing by Wolters Kluwer Health.

37. Attached hereto as Appendix STEDMAN01 is a true and correct copy of the MARC record for Stedman's Medical Dictionary for the Health Professions and Nursing as held by the Carnegie Library of Pittsburgh. I secured this record myself from the library's public catalog. The MARC record contained within Appendix STEDMAN01 accurately describes the title, author, publisher, and ISBN number of Stedman's Medical Dictionary for the Health Professions and Nursing.

38. Attached hereto as Appendix STEDMAN02 is a true and correct copy of Stedman's Medical Dictionary for the Health Professions and Nursing as held by the Carnegie Library of Pittsburgh. These scans were secured from the library's collection. In comparing Exhibit 2018 to Appendix STEDMAN02, it is my determination that Exhibit 2018 is a true and correct copy of Stedman's Medical Dictionary for the Health Professions and Nursing by Wolters Kluwer Health.

39. The 008 field of the MARC record in Appendix STEDMAN01 indicates the date of record creation. The 008 field of Appendix STEDMAN01 indicates the Carnegie Library of Pittsburgh first acquired Stedman's Medical

Dictionary for the Health Professions and Nursing as of February 4, 2011. Considering this information, it is my determination that Stedman's Medical Dictionary for the Health Professions and Nursing was made available to the public shortly after its initial acquisition as of February 4, 2011.

K. Taber's Dictionary (Ex. 2019)

40. I have reviewed Exhibit 2019, Taber's Cyclopedic Medical Dictionary by Donald Venes.

41. Attached hereto as Appendix TABER01 is a true and correct copy of the MARC record for Taber's Cyclopedic Medical Dictionary as held by the Penn State University Library. I secured this record myself from the library's public catalog. The MARC record contained within Appendix TABER01 accurately describes the title, author, publisher, and ISBN number of Taber's Cyclopedic Medical Dictionary.

42. Attached hereto as Appendix TABER02 is a true and correct copy of Taber's Cyclopedic Medical Dictionary as held by the Penn State University Library. This PDF was secured from the library's collection. In comparing Exhibit 2019 to Appendix TABER02, it is my determination that Exhibit 2019 is a true and correct copy of Taber's Cyclopedic Medical Dictionary by Donald Venes.

43. The 008 field of the MARC record in Appendix TABER01 indicates the date of record creation. The 008 field of Appendix TABER01 indicates the Penn

State University Library first acquired Taber's Cyclopedic Medical Dictionary as of August 21, 2012. Considering this information, it is my determination that Taber's Cyclopedic Medical Dictionary was made available to the public shortly after its initial acquisition as of August 21, 2012.

L. Undevia (Ex. 2023)

44. I have reviewed Exhibit 2023, "Pharmacokinetic Variability of Anticancer Agents" by Samir D. Undevia, et al. as published in Nature Reviews Cancer June 2005.

45. Attached hereto as Appendix UNDEVIA01 is a true and correct copy of the MARC record for Nature Reviews Cancer as held by the Penn State University Library. I secured this record myself from the library's public catalog. The MARC record contained within Appendix UNDEVIA01 accurately describes the title, publisher and ISSN number of Nature Reviews Cancer. The Showing Results field present on page 3 of this record indicates the library's collection includes the June 2005 issue of Nature Reviews Cancer containing "Pharmacokinetic Variability of Anticancer Agents."

46. Attached hereto as Appendix UNDEVIA02 is a true and correct copy of "Pharmacokinetic Variability of Anticancer Agents" as published in Nature Reviews Cancer as held by the Penn State University Library. This PDF was secured from the library's collection. In comparing Exhibit 2023 to Appendix

UNDEVIA02, it is my determination that Exhibit 2023 is a true and correct copy of “Pharmacokinetic Variability of Anticancer Agents” by Samir D. Undevia, et al. as published in Nature Reviews Cancer.

47. The 008 field of the MARC record in Appendix UNDEVIA01 indicates the date of record creation. The 008 field of Appendix UNDEVIA01 indicates the Penn State University Library first acquired Nature Reviews Cancer as of June 15, 2001 and held the journal in perpetuity until the publication of “Pharmacokinetic Variability of Anticancer Agents.” Considering this information, it is my determination that Nature Reviews Cancer June 2005 and therefore “Pharmacokinetic Variability of Anticancer Agents” was made available to the public shortly after its initial publication in June 2005.

M. Ratain 2014 (Ex. 2025)

48. I have reviewed Exhibit 2025, “Dose-Finding and Pharmokinetic Study to Optimize the Dosing of Irinotecan According to the UGT1A1 Genotype of Patients with Cancer” by Federico Innocenti, et al as published in Journal of Clinical Oncology August 1, 2014.

49. Attached hereto as Appendix JCO01 is a true and correct copy of the MARC record for Journal of Clinical Oncology as held by the University of Toronto Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix JCO01 accurately describes the title, publisher

and ISSN number of Journal of Clinical Oncology. The View Online field present on page 2 of this record indicates the library's collection includes the August 1, 2014 issue of Journal of Clinical Oncology containing “Dose-Finding and Pharmacokinetic Study to Optimize the Dosing of Irinotecan According to the UGT1A1 Genotype of Patients with Cancer.”

50. Attached hereto as Appendix RATAIN04 is a true and correct copy of “Dose-Finding and Pharmacokinetic Study to Optimize the Dosing of Irinotecan According to the UGT1A1 Genotype of Patients with Cancer” as published in Journal of Clinical Oncology as held by the University of Toronto Library. This PDF was secured from the library’s collection. In comparing Exhibit 2025 to Appendix RATAIN04, it is my determination that Exhibit 2025 is a true and correct copy of “Dose-Finding and Pharmacokinetic Study to Optimize the Dosing of Irinotecan According to the UGT1A1 Genotype of Patients with Cancer” by Federico Innocenti, et al. as published in Journal of Clinical Oncology.

51. The 008 field of the MARC record in Appendix JCO01 indicates the date of record creation. The 008 field of Appendix JCO01 indicates the University of Toronto Library first acquired Journal of Clinical Oncology as of December 10, 1999 and held the journal in perpetuity until the publication of “Dose-Finding and Pharmacokinetic Study to Optimize the Dosing of Irinotecan According to the UGT1A1 Genotype of Patients with Cancer.” Considering this information, it is my

determination that Journal of Clinical Oncology August 1, 2014 and therefore “Dose-Finding and Pharmacokinetic Study to Optimize the Dosing of Irinotecan According to the UGT1A1 Genotype of Patients with Cancer” was made available to the public shortly after its initial publication as of August 1, 2014.

N. Bach (Ex. 2026)

52. I have reviewed Exhibit 2026, “Therapeutic Drug Monitoring in Cancer Chemotherapy” by Dylan M. Bach, et al as published in Bioanalysis May 2010.

53. Attached hereto as Appendix BACH01 is a true and correct copy of the MARC record for Bioanalysis as held by the University of Toronto Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix BACH01 accurately describes the title, publisher and ISSN number of Bioanalysis. The View Online field present on page 2 of this record indicates the library's collection includes the May 2010 issue of Bioanalysis containing “Therapeutic Drug Monitoring in Cancer Chemotherapy.”

54. Attached hereto as Appendix BACH02 is a true and correct copy of “Therapeutic Drug Monitoring in Cancer Chemotherapy” as published in Bioanalysis as held by the University of Toronto Library. These scans were secured from the library’s collection. In comparing Exhibit 2026 to Appendix BACH02, it is my determination that Exhibit 2026 is a true and correct copy of “Therapeutic

Drug Monitoring in Cancer Chemotherapy” by Dylan M. Bach, et al as published in Bioanalysis.

55. The 008 field of the MARC record in Appendix BACH01 indicates the date of record creation. The 008 field of Appendix BACH01 indicates the University of Toronto Library first acquired Bioanalysis as of April 28, 2008 and held the journal in perpetuity until the publication of “Therapeutic Drug Monitoring in Cancer Chemotherapy.” Considering this information, it is my determination that Bioanalysis May 2010 and therefore “Therapeutic Drug Monitoring in Cancer Chemotherapy” was made available to the public shortly after its initial publication in May 2010.

O. Gurney (Ex. 2027)

56. I have reviewed Exhibit 2027, “How to Calculate the Dose of Chemotherapy” by H. Gurney as published in British Journal of Cancer April 22, 2002.

57. Attached hereto as Appendix BJC01 is a true and correct copy of the MARC record for British Journal of Cancer as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix BJC01 accurately describes the title, publisher and ISSN number of British Journal of Cancer. The Showing Results field present on page 3 of this record indicates the library's collection includes the April 22, 2002

issue of British Journal of Cancer containing “How to Calculate the Dose of Chemotherapy.”

58. Attached hereto as Appendix GURNEY01 is a true and correct copy of “How to Calculate the Dose of Chemotherapy” as published in British Journal of Cancer as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2027 to Appendix GURNEY01, it is my determination that Exhibit 2027 is a true and correct copy of “How to Calculate the Dose of Chemotherapy” by H. Gurney as published in British Journal of Cancer.

59. The 008 field of the MARC record in Appendix BJC01 indicates the date of record creation. The 008 field of Appendix BJC01 indicates the Penn State University Library first acquired British Journal of Cancer as of June 12, 2000 and held the journal in perpetuity until the publication of “How to Calculate the Dose of Chemotherapy.” Considering this information, it is my determination that British Journal of Cancer April 22, 2002 and therefore “How to Calculate the Dose of Chemotherapy” was made available to the public shortly after its initial publication as of April 22, 2002.

P. Alnaim (Ex. 2028)

60. I have reviewed Exhibit 2028, “Therapeutic Drug Monitoring of Cancer Chemotherapy” by Lamya Alnaim as published in Journal of Oncology Pharmacy Practice December 2007.

61. Attached hereto as Appendix ALNAIM01 is a true and correct copy of the MARC record for Journal of Oncology Pharmacy Practice as held by the Penn State University Library. I secured this record myself from the library's public catalog. The MARC record contained within Appendix ALNAIM01 accurately describes the title, publisher and ISSN number of Journal of Oncology Pharmacy Practice. The Showing Results field present on page 3 of this record indicates the library's collection includes the December 2007 issue of Journal of Oncology Pharmacy Practice containing "Therapeutic Drug Monitoring of Cancer Chemotherapy."

62. Attached hereto as Appendix ALNAIM02 is a true and correct copy of "Therapeutic Drug Monitoring of Cancer Chemotherapy" as published in Journal of Oncology Pharmacy Practice as held by the Penn State University Library. This PDF was secured from the library's collection. In comparing Exhibit 2028 to Appendix ALNAIM02, it is my determination that Exhibit 2028 is a true and correct copy of "Therapeutic Drug Monitoring of Cancer Chemotherapy" by Lamya Alnaim as published in Journal of Oncology Pharmacy Practice.

63. The 008 field of the MARC record in Appendix ALNAIM01 indicates the date of record creation. The 008 field of Appendix ALNAIM01 indicates the Penn State University Library first acquired Journal of Oncology Pharmacy Practice as of February 24, 2000 and held the journal in perpetuity until the publication of

“Therapeutic Drug Monitoring of Cancer Chemotherapy.” Considering this information, it is my determination that Journal of Oncology Pharmacy Practice December 2007 and therefore “Therapeutic Drug Monitoring of Cancer Chemotherapy” was made available to the public shortly after its initial publication in December 2007.

Q. Jiao (Ex. 2029)

64. I have reviewed Exhibit 2029, “Comparative Effectiveness of NALIRIFOX vs. FOLFIRINOX in Pancreatic Cancer” by Xiayu Jiao, et al. as published in American Journal of Clinical Oncology May 29, 2024.

65. Attached hereto as Appendix JIAO01 is a true and correct copy of the MARC record for American Journal of Clinical Oncology as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix JIAO01 accurately describes the title, publisher and ISSN number of American Journal of Clinical Oncology. The Showing Results field present on page 3 of this record indicates the library's collection includes the May 29, 2024 issue of American Journal of Clinical Oncology containing “Comparative Effectiveness of NALIRIFOX vs. FOLFIRINOX in Pancreatic Cancer.”

66. Attached hereto as Appendix JIAO02 is a true and correct copy of “Comparative Effectiveness of NALIRIFOX vs. FOLFIRINOX in Pancreatic

Cancer” as published in American Journal of Clinical Oncology as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2029 to Appendix JIAO02, it is my determination that Exhibit 2029 is a true and correct copy of “Comparative Effectiveness of NALIRIFOX vs. FOLFIRINOX in Pancreatic Cancer” by Xiayu Jiao, et al. as published in American Journal of Clinical Oncology.

67. The 008 field of the MARC record in Appendix JIAO01 indicates the date of record creation. The 008 field of Appendix JIAO01 indicates the Penn State University Library first acquired American Journal of Clinical Oncology as of July 24, 2001 and held the journal in perpetuity until the publication of “Comparative Effectiveness of NALIRIFOX vs. FOLFIRINOX in Pancreatic Cancer.” Considering this information, it is my determination that American Journal of Clinical Oncology May 29, 2024 and therefore “Comparative Effectiveness of NALIRIFOX vs. FOLFIRINOX in Pancreatic Cancer” was made available to the public shortly after its initial publication as of May 29, 2024.

R. Xiang (Ex. 2030)

68. I have reviewed Exhibit 2030, “Cost-effectiveness Analysis of First-Line Combination Chemotherapy Regimens for Metastatic Pancreatic Cancer and Evidence-based Pricing Strategy of Liposomal Irinotecan in China” by Zuojuan Xiang, et al. as published in Frontiers in Pharmacology December 2024.

69. Attached hereto as Appendix XIANG01 is a true and correct copy of the MARC record for Frontiers in Pharmacology as held by the Penn State University Library. I secured this record myself from the library's public catalog. The MARC record contained within Appendix XIANG01 accurately describes the title, publisher and ISSN number of Frontiers in Pharmacology. The Showing Results field present on page 3 of this record indicates the library's collection includes the December 2024 issue of Frontiers in Pharmacology containing "Cost-effectiveness Analysis of First-Line Combination Chemotherapy Regimens for Metastatic Pancreatic Cancer and Evidence-based Pricing Strategy of Liposomal Irinotecan in China."

70. Attached hereto as Appendix XIANG02 is a true and correct copy of "Cost-effectiveness Analysis of First-Line Combination Chemotherapy Regimens for Metastatic Pancreatic Cancer and Evidence-based Pricing Strategy of Liposomal Irinotecan in China" as published in Frontiers in Pharmacology as held by the Penn State University Library. This PDF was secured from the library's collection. In comparing Exhibit 2030 to Appendix XIANG02, it is my determination that Exhibit 2030 is a true and correct copy of "Cost-effectiveness Analysis of First-Line Combination Chemotherapy Regimens for Metastatic Pancreatic Cancer and Evidence-based Pricing Strategy of Liposomal Irinotecan in China" by Zuojuan Xiang, et al. as published in Frontiers in Pharmacology.

71. The 008 field of the MARC record in Appendix XIANG01 indicates the date of record creation. The 008 field of Appendix XIANG01 indicates the Penn State University Library first acquired *Frontiers in Pharmacology* as of December 3, 2010 and held the journal in perpetuity until the publication of “Cost-effectiveness Analysis of First-Line Combination Chemotherapy Regimens for Metastatic Pancreatic Cancer and Evidence-based Pricing Strategy of Liposomal Irinotecan in China.” Considering this information, it is my determination that *Frontiers in Pharmacology* December 2024 and therefore “Cost-effectiveness Analysis of First-Line Combination Chemotherapy Regimens for Metastatic Pancreatic Cancer and Evidence-based Pricing Strategy of Liposomal Irinotecan in China” was made available to the public shortly after its initial publication in December 2024.

S. Cockrum (Ex. 2031)

72. I have reviewed Exhibit 2031, “Overall Survival (OS) of Patients with Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Treated with First-Line (1L) FOLFIRINOX (FFX): Bridging the Gap Between the NAPOLI 3 Trial and Real-World Practice” by Paul Cockrum, et al as published in *Journal of Clinical Oncology* January 25, 2025.

73. Attached hereto as Appendix JCO01 is a true and correct copy of the MARC record for *Journal of Clinical Oncology* as held by the University of Toronto Library. I secured this record myself from the library’s public catalog. The MARC

record contained within Appendix JCO01 accurately describes the title, publisher and ISSN number of Journal of Clinical Oncology. The View Online field present on page 2 of this record indicates the library's collection includes the January 25, 2025 issue of Journal of Clinical Oncology containing “Overall Survival (OS) of Patients with Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Treated with First-Line (1L) FOLFIRINOX (FFX): Bridging the Gap Between the NAPOLI 3 Trial and Real-World Practice.”

74. Attached hereto as Appendix COCKRUM01 is a true and correct copy of “Overall Survival (OS) of Patients with Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Treated with First-Line (1L) FOLFIRINOX (FFX): Bridging the Gap Between the NAPOLI 3 Trial and Real-World Practice” as published in Journal of Clinical Oncology as held by the University of Toronto Library. This PDF was secured from the library’s collection. In comparing Exhibit 2031 to Appendix COCKRUM01, it is my determination that Exhibit 2031 is a true and correct copy of “Overall Survival (OS) of Patients with Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Treated with First-Line (1L) FOLFIRINOX (FFX): Bridging the Gap Between the NAPOLI 3 Trial and Real-World Practice” by Paul Cockrum, et al. as published in Journal of Clinical Oncology.

75. The 008 field of the MARC record in Appendix JCO01 indicates the date of record creation. The 008 field of Appendix JCO01 indicates the University

of Toronto Library first acquired Journal of Clinical Oncology as of December 10, 1999 and held the journal in perpetuity until the publication of “Overall Survival (OS) of Patients with Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Treated with First-Line (1L) FOLFIRINOX (FFX): Bridging the Gap Between the NAPOLI 3 Trial and Real-World Practice.” Considering this information, it is my determination that Journal of Clinical Oncology January 25, 2025 and therefore “Overall Survival (OS) of Patients with Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) Treated with First-Line (1L) FOLFIRINOX (FFX): Bridging the Gap Between the NAPOLI 3 Trial and Real-World Practice” was made available to the public shortly after its initial publication as of January 25, 2025.

T. Wainberg 2023 (Ex. 2032)

76. I have reviewed Exhibit 2032, “NALIRIFOX versus Nab-paclitaxel and Gemcitabine in Treatment-naïve Patients with Metastatic Pancreatic Ductal Adenocarcinoma (NAPOLI 3): A Randomised, Open-Label, Phase 3 Trial” by Zev A. Wainberg, et al. as published in Lancet October 7, 2023.

77. Attached hereto as Appendix WAINBERG02 is a true and correct copy of the MARC record for Lancet as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix WAINBERG02 accurately describes the title, publisher and ISSN number of Lancet. The Showing Results field present on page 3 of this

record indicates the library's collection includes the October 7, 2023 issue of Lancet containing “NALIRIFOX versus Nab-paclitaxel and Gemcitabine in Treatment-naive Patients with Metastatic Pancreatic Ductal Adenocarcinoma (NAPOLI 3): A Randomised, Open-Label, Phase 3 Trial.”

78. Attached hereto as Appendix WAINBERG03 is a true and correct copy of “NALIRIFOX versus Nab-paclitaxel and Gemcitabine in Treatment-naive Patients with Metastatic Pancreatic Ductal Adenocarcinoma (NAPOLI 3): A Randomised, Open-Label, Phase 3 Trial” as published in Lancet as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2032 to Appendix WAINBERG03, it is my determination that Exhibit 2032 is a true and correct copy of “NALIRIFOX versus Nab-paclitaxel and Gemcitabine in Treatment-naive Patients with Metastatic Pancreatic Ductal Adenocarcinoma (NAPOLI 3): A Randomised, Open-Label, Phase 3 Trial” by Zev A. Wainberg, et al. as published in Lancet.

79. The 008 field of the MARC record in Appendix WAINBERG02 indicates the date of record creation. The 008 field of Appendix WAINBERG02 indicates the Penn State University Library first acquired Lancet as of April 2, 1999 and held the journal in perpetuity until the publication of “NALIRIFOX versus Nab-paclitaxel and Gemcitabine in Treatment-naive Patients with Metastatic Pancreatic Ductal Adenocarcinoma (NAPOLI 3): A Randomised, Open-Label, Phase 3 Trial.”

Considering this information, it is my determination that Lancet October 7, 2023 and therefore “NALIRIFOX versus Nab-paclitaxel and Gemcitabine in Treatment-naive Patients with Metastatic Pancreatic Ductal Adenocarcinoma (NAPOLI 3): A Randomised, Open-Label, Phase 3 Trial” was made available to the public shortly after its initial publication as of October 7, 2023.

U. Skorupan (Ex. 2033)

80. I have reviewed Exhibit 2033, a document entitled First-Line Treatment of Metastatic Pancreatic Ductal Adenocarcinoma: Did 2024 Offer New Insights?

81. Attached hereto as Appendix SKORUPAN01 is a screen capture of a webpage entitled First-Line Treatment of Metastatic Pancreatic Ductal Adenocarcinoma: Did 2024 Offer New Insights? as hosted on the ASCO Daily News website. I secured these screen captures myself from <https://dailynews.ascopubs.org/do/first-line-treatment-metastatic-pancreatic-ductal-adenocarcinoma-did-2024-offer-new>. In comparing Appendix SKORUPAN01 to Exhibit 2033, it is my determination Exhibit 2033 is a true and correct copy of First-Line Treatment of Metastatic Pancreatic Ductal Adenocarcinoma: Did 2024 Offer New Insights? As the dateline visible on page 1 of Appendix SKORUPAN01 and Exhibit 2033 reads January 22, 2025, it is my determination Exhibit 2033 was likely made available to the public as of January 22, 2025.

V. Kobayashi (Ex. 2034)

82. I have reviewed Exhibit 2034, “GnP vs mFOLFIRINOX or S-IROX in Metastatic Pancreatic Cancer: 1-year Follow-up Updated Data from the Generate (JCOG1611)” by S. Kobayashi, et al. as published in Annals of Oncology September 2024.

83. Attached hereto as Appendix AO01 is a true and correct copy of the MARC record for Annals of Oncology as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix AO01 accurately describes the title, publisher and ISSN number of Annals of Oncology. The Showing Results field present on page 3 of this record indicates the library's collection includes the September 2024 issue of Annals of Oncology containing “GnP vs mFOLFIRINOX or S-IROX in Metastatic Pancreatic Cancer: 1-year Follow-up Updated Data from the Generate (JCOG1611).”

84. Attached hereto as Appendix KOBAYASHI01 is a true and correct copy of “GnP vs mFOLFIRINOX or S-IROX in Metastatic Pancreatic Cancer: 1-year Follow-up Updated Data from the Generate (JCOG1611)” as published in Annals of Oncology as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2034 to Appendix KOBAYASHI01, it is my determination that Exhibit 2034 is a true and correct copy

of “GnP vs mFOLFIRINOX or S-IROX in Metastatic Pancreatic Cancer: 1-year Follow-up Updated Data from the Generate (JCOG1611)” by S. Kobayashi, et al. as published in Annals of Oncology.

85. The 008 field of the MARC record in Appendix AO01 indicates the date of record creation. The 008 field of Appendix AO01 indicates the Penn State University Library first acquired Annals of Oncology as of June 16, 1999 and held the journal in perpetuity until the publication of “GnP vs mFOLFIRINOX or S-IROX in Metastatic Pancreatic Cancer: 1-year Follow-up Updated Data from the Generate (JCOG1611).” Considering this information, it is my determination that Annals of Oncology September 2024 and therefore “GnP vs mFOLFIRINOX or S-IROX in Metastatic Pancreatic Cancer: 1-year Follow-up Updated Data from the Generate (JCOG1611)” was made available to the public shortly after its initial publication in September 2024.

W. NCCN Guidelines 2015 (Ex. 2036)

86. I have reviewed Exhibit 2036, a document entitled NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma Version 2.2015.

87. Attached hereto as Appendix NCCN01 is a screen capture of the Internet Archive Wayback Machine entry for <http://www.tri-kobe.org/nccn/guideline/archive/index.html>. I secured these screen captures myself from <https://web.archive.org/web/20170402115847/http://www.tri->

kobe.org/nccn/guideline/archive/index.html. This record was captured as of April 2, 2017.

88. Appendix NCCN01 is an Internet Archive capture of a web page entitled NCCNガイドライン日本語版 アーカイブ as hosted on the Tri-Kobe.org website. Appendix NCCN01 is a capture of a web page that hosts English-language and Japanese-language NCCN guidelines documents. Page 4 of Appendix NCCN01 contains an entry for the 2.2015 version of NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma, including a link to download an English-language copy of these guidelines. As this webpage was captured by the Internet Archive as of April 2, 2017, it is my determination that NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma Version 2.2015 was available the public no later than April 2, 2017.

89. Attached hereto as Appendix NCCN02 is a screen capture of the Internet Archive Wayback Machine entry for <https://www2.tri-kobe.org/nccn/guideline/archive/pancreas2015/english/pancreatic.pdf>. I secured these screen captures myself from <https://web.archive.org/web/20170402115847/http://www.tri-kobe.org/nccn/guideline/archive/index.html>. This record was captured as of February 2, 2023.

90. Appendix NCCN02 is an Internet Archive capture of a file entitled NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma Version 2.2015 as hosted on the Tri-Kobe.org website. In comparing Appendix NCCN02 to Exhibit 2036, it is my determination that Exhibit 2036 is a true and correct copy of NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma Version 2.2015.

X. Ratain 2009 (Ex. 2037)

91. I have reviewed Exhibit 2037, “Optimising the Design of Phase II Oncology Trials: The Importance of Randomisation” by Mark J. Ratain, et al. as published in European Journal of Cancer August 2008.

92. Attached hereto as Appendix EJC01 is a true and correct copy of the MARC record for European Journal of Cancer as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix EJC01 accurately describes the title, publisher and ISSN number of European Journal of Cancer. The Showing Results field present on page 3 of this record indicates the library's collection includes the August 2008 issue of European Journal of Cancer containing “Optimising the Design of Phase II Oncology Trials: The Importance of Randomisation.”

93. Attached hereto as Appendix RATAIN03 is a true and correct copy of “Optimising the Design of Phase II Oncology Trials: The Importance of

Randomisation” as published in European Journal of Cancer as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2037 to Appendix RATAIN03, it is my determination that Exhibit 2037 is a true and correct copy of “Optimising the Design of Phase II Oncology Trials: The Importance of Randomisation” by Mark J. Ratain, et al. as published in European Journal of Cancer.

94. The 008 field of the MARC record in Appendix EJC01 indicates the date of record creation. The 008 field of Appendix EJC01 indicates the Penn State University Library first acquired European Journal of Cancer as of January 29, 2001 and held the journal in perpetuity until the publication of “Optimising the Design of Phase II Oncology Trials: The Importance of Randomisation.” Considering this information, it is my determination that European Journal of Cancer August 2008 and therefore “Optimising the Design of Phase II Oncology Trials: The Importance of Randomisation” was made available to the public shortly after its initial publication in August 2008.

Y. Ychou (Ex. 2038)

95. I have reviewed Exhibit 2038, “An Open Phase I Study Assessing the Feasibility of the Triple Combination: Oxaliplatin Plus Irinotecan Plus Leucovorin/5-fluorouracil Every 2 Weeks in Patients with Advanced Solid Tumors” by M. Ychou, et al. as published in Annals of Oncology March 2003.

96. Attached hereto as Appendix YCHOU01 is a true and correct copy of “An Open Phase I Study Assessing the Feasibility of the Triple Combination: Oxaliplatin Plus Irinotecan Plus Leucovorin/5-fluorouracil Every 2 Weeks in Patients with Advanced Solid Tumors” as published in Annals of Oncology as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2038 to Appendix YCHOU01, it is my determination that Exhibit 2038 is a true and correct copy of “An Open Phase I Study Assessing the Feasibility of the Triple Combination: Oxaliplatin Plus Irinotecan Plus Leucovorin/5-fluorouracil Every 2 Weeks in Patients with Advanced Solid Tumors” by M. Ychou, et al. as published in Annals of Oncology.

97. Attached hereto as Appendix AO01 is a true and correct copy of the MARC record for Annals of Oncology as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix AO01 accurately describes the title, publisher and ISSN number of Annals of Oncology. The Showing Results field present on page 3 of this record indicates the library’s collection includes the March 2003 issue of Annals of Oncology containing “An Open Phase I Study Assessing the Feasibility of the Triple Combination: Oxaliplatin Plus Irinotecan Plus Leucovorin/5-fluorouracil Every 2 Weeks in Patients with Advanced Solid Tumors.”

98. The 008 field of the MARC record in Appendix AO01 indicates the date of record creation. The 008 field of Appendix AO01 indicates the Penn State University Library first acquired Annals of Oncology as of June 16, 1999 and held the journal in perpetuity until the publication of “An Open Phase I Study Assessing the Feasibility of the Triple Combination: Oxaliplatin Plus Irinotecan Plus Leucovorin/5-fluorouracil Every 2 Weeks in Patients with Advanced Solid Tumors.” Considering this information, it is my determination that Annals of Oncology March 2003 and therefore “An Open Phase I Study Assessing the Feasibility of the Triple Combination: Oxaliplatin Plus Irinotecan Plus Leucovorin/5-fluorouracil Every 2 Weeks in Patients with Advanced Solid Tumors” was made available to the public shortly after its initial publication in March 2003.

Z. Gourgou-Bourgade (Ex. 2039)

99. I have reviewed Exhibit 2039, “Impact of FOLFIRINOX Compared With Gemcitabine on Quality of Life in Patients With Metastatic Pancreatic Cancer: Results From the PRODIGE 4/ACCORD 11 Randomized Trial” by Sophie Gourgou-Bourgade, et al as published in Journal of Clinical Oncology January 1, 2013.

100. Attached hereto as Appendix JCO01 is a true and correct copy of the MARC record for Journal of Clinical Oncology as held by the University of Toronto Library. I secured this record myself from the library’s public catalog. The MARC

record contained within Appendix JCO01 accurately describes the title, publisher and ISSN number of Journal of Clinical Oncology. The View Online field present on page 2 of this record indicates the library's collection includes the January 1, 2013 issue of Journal of Clinical Oncology containing "Impact of FOLFIRINOX Compared With Gemcitabine on Quality of Life in Patients With Metastatic Pancreatic Cancer: Results From the PRODIGE 4/ACCORD 11 Randomized Trial."

101. Attached hereto as Appendix GOURGOU01 is a true and correct copy of "Impact of FOLFIRINOX Compared With Gemcitabine on Quality of Life in Patients With Metastatic Pancreatic Cancer: Results From the PRODIGE 4/ACCORD 11 Randomized Trial" as published in Journal of Clinical Oncology as held by the University of Toronto Library. This PDF was secured from the library's collection. In comparing Exhibit 2039 to Appendix GOURGOU01, it is my determination that Exhibit 2039 is a true and correct copy of "Impact of FOLFIRINOX Compared With Gemcitabine on Quality of Life in Patients With Metastatic Pancreatic Cancer: Results From the PRODIGE 4/ACCORD 11 Randomized Trial" by Sophie Gourgou-Bourgade, et al as published in Journal of Clinical Oncology.

102. The 008 field of the MARC record in Appendix JCO01 indicates the date of record creation. The 008 field of Appendix JCO01 indicates the University of Toronto Library first acquired Journal of Clinical Oncology as of December 10,

1999 and held the journal in perpetuity until the publication of “Impact of FOLFIRINOX Compared With Gemcitabine on Quality of Life in Patients With Metastatic Pancreatic Cancer: Results From the PRODIGE 4/ACCORD 11 Randomized Trial.” Considering this information, it is my determination that Journal of Clinical Oncology January 1, 2013 and therefore “Impact of FOLFIRINOX Compared With Gemcitabine on Quality of Life in Patients With Metastatic Pancreatic Cancer: Results From the PRODIGE 4/ACCORD 11 Randomized Trial” was made available to the public shortly after its initial publication as of January 1, 2013.

AA. FDA Approval Letter (Ex. 2040)

103. I have reviewed Exhibit 2040, a document entitled NA 207793/S-016.

104. Attached hereto as Appendix FDA01 is a screen capture of the Internet Archive Wayback Machine entry for https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2024/207793Orig1s016ltr.pdf. I secured these screen captures myself from https://web.archive.org/web/20240225224600/https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2024/207793Orig1s016ltr.pdf. This record was captured as of February 25, 2024.

105. Appendix FDA01 is an Internet Archive capture of a file entitled NA 207793/S-016 as hosted on the FDA website. In comparing Appendix FDA01 to

Exhibit 2040, it is my determination that Exhibit 2040 is a true and correct copy of NA 207793/S-016 as hosted on the FDA website. As the Internet Archive first captured this file as of February 25, 2024, it is my determination that NA 207793/S-016 was first made available to the public as of February 25, 2024 via the Internet Archive and likely earlier via the original FDA website.

BB. Oh (Ex. 2041)

106. I have reviewed Exhibit 2041, “Pilot Study of Irinotecan/Xalipitin (IROX) Combination Chemotherapy for Patients with Gemcitabine- and 5-fluorouracil-refractory Pancreatic Cancer” by Sung Yong Oh, et al. as published in Investigational New Drugs June 2010.

107. Attached hereto as Appendix OH01 is a true and correct copy of the MARC record for Investigational New Drugs as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix OH01 accurately describes the title, publisher and ISSN number of Investigational New Drugs. The Showing Results field present on page 3 of this record indicates the library's collection includes the June 2010 issue of Investigational New Drugs containing “Pilot Study of Irinotecan/Xalipitin (IROX) Combination Chemotherapy for Patients with Gemcitabine- and 5-fluorouracil-refractory Pancreatic Cancer.”

108. Attached hereto as Appendix OH02 is a true and correct copy of “Pilot Study of Irinotecan/Xalipitin (IROX) Combination Chemotherapy for Patients with Gemcitabine- and 5-fluorouracil-refractory Pancreatic Cancer” as published in Investigational New Drugs as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2041 to Appendix OH02, it is my determination that Exhibit 2041 is a true and correct copy of “Pilot Study of Irinotecan/Xalipitin (IROX) Combination Chemotherapy for Patients with Gemcitabine- and 5-fluorouracil-refractory Pancreatic Cancer” by Sung Yong Oh, et al. as published in Investigational New Drugs.

109. The 008 field of the MARC record in Appendix OH01 indicates the date of record creation. The 008 field of Appendix OH01 indicates the Penn State University Library first acquired Investigational New Drugs as of June 18, 1999 and held the journal in perpetuity until the publication of “Pilot Study of Irinotecan/Xalipitin (IROX) Combination Chemotherapy for Patients with Gemcitabine- and 5-fluorouracil-refractory Pancreatic Cancer.” Considering this information, it is my determination that Investigational New Drugs June 2010 and therefore “Pilot Study of Irinotecan/Xalipitin (IROX) Combination Chemotherapy for Patients with Gemcitabine- and 5-fluorouracil-refractory Pancreatic Cancer” was made available to the public shortly after its initial publication in June 2010.

CC. Zhang (Ex. 2042)

110. I have reviewed Exhibit 2042, “Oxaliplatin plus Irinotecan vs Irinotecan as Second-line Treatment in Pancreatic Cancer Patients: a Randomized–controlled Open-label Phase II Study” by Hangyu Zhang, et al. as published in Gastroenterology Report February 3, 2023.

111. Attached hereto as Appendix ZHANG01 is a true and correct copy of the MARC record for Gastroenterology Report as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix ZHANG01 accurately describes the title, publisher and ISSN number of Gastroenterology Report. The Showing Results field present on page 3 of this record indicates the library's collection includes the February 3, 2023 issue of Gastroenterology Report containing “Oxaliplatin plus Irinotecan vs Irinotecan as Second-line Treatment in Pancreatic Cancer Patients: a Randomized–controlled Open-label Phase II Study.”

112. Attached hereto as Appendix ZHANG02 is a true and correct copy of “Oxaliplatin plus Irinotecan vs Irinotecan as Second-line Treatment in Pancreatic Cancer Patients: a Randomized–controlled Open-label Phase II Study” as published in Gastroenterology Report as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2042 to Appendix ZHANG02, it is my determination that Exhibit 2042 is a true and correct copy of

“Oxaliplatin plus Irinotecan vs Irinotecan as Second-line Treatment in Pancreatic Cancer Patients: a Randomized–controlled Open-label Phase II Study” by Hangyu Zhang, et al. as published in Gastroenterology Report.

113. The 008 field of the MARC record in Appendix ZHANG01 indicates the date of record creation. The 008 field of Appendix ZHANG01 indicates the Penn State University Library first acquired Gastroenterology Report as of June 7, 2013 and held the journal in perpetuity until the publication of “Oxaliplatin plus Irinotecan vs Irinotecan as Second-line Treatment in Pancreatic Cancer Patients: a Randomized–controlled Open-label Phase II Study.” Considering this information, it is my determination that Gastroenterology Report February 3, 2023 and therefore “Oxaliplatin plus Irinotecan vs Irinotecan as Second-line Treatment in Pancreatic Cancer Patients: a Randomized–controlled Open-label Phase II Study” was made available to the public shortly after its initial publication as of February 3, 2023.

DD. Gunturu (Ex. 2043)

114. I have reviewed Exhibit 2043, “FOLFIRINOX for Locally Advanced and Metastatic Pancreatic Cancer: Single Institution Retrospective Review of Efficacy and Toxicity” by Krishna S. Gunturu, et al as published in Medical Oncology March 2013.

115. Attached hereto as Appendix GUNTURU01 is a true and correct copy of the MARC record for Medical Oncology as held by the Penn State University

Library. I secured this record myself from the library's public catalog. The MARC record contained within Appendix GUNTURU01 accurately describes the title, publisher and ISSN number of Medical Oncology. The Showing Results field present on page 3 of this record indicates the library's collection includes the March 2013 issue of Medical Oncology containing "FOLFIRINOX for Locally Advanced and Metastatic Pancreatic Cancer: Single Institution Retrospective Review of Efficacy and Toxicity."

116. Attached hereto as Appendix GUNTURU02 is a true and correct copy of "FOLFIRINOX for Locally Advanced and Metastatic Pancreatic Cancer: Single Institution Retrospective Review of Efficacy and Toxicity" as published in Medical Oncology as held by the Penn State University Library. This PDF was secured from the library's collection. In comparing Exhibit 2043 to Appendix GUNTURU02, it is my determination that Exhibit 2043 is a true and correct copy of "FOLFIRINOX for Locally Advanced and Metastatic Pancreatic Cancer: Single Institution Retrospective Review of Efficacy and Toxicity" by Krishna S. Gunturu, et al as published in Medical Oncology.

117. The 008 field of the MARC record in Appendix GUNTURU01 indicates the date of record creation. The 008 field of Appendix GUNTURU01 indicates the Penn State University Library first acquired Medical Oncology as of October 15, 1997 and held the journal in perpetuity until the publication of

“FOLFIRINOX for Locally Advanced and Metastatic Pancreatic Cancer: Single Institution Retrospective Review of Efficacy and Toxicity.” Considering this information, it is my determination that Medical Oncology March 2013 and therefore “FOLFIRINOX for Locally Advanced and Metastatic Pancreatic Cancer: Single Institution Retrospective Review of Efficacy and Toxicity” was made available to the public shortly after its initial publication in March 2013.

EE. Amiri-Kordestani (Ex. 2044)

118. I have reviewed Exhibit 2044, “Why Do Phase III Clinical Trials in Oncology Fail so Often?” by Laleh Amiri-Kordestani as published in JNCI April 18, 2012.

119. Attached hereto as Appendix AMIRI01 is a true and correct copy of the MARC record for JNCI as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix AMIRI01 accurately describes the title, publisher and ISSN number of JNCI. The Showing Results field present on page 3 of this record indicates the library's collection includes the April 18, 2012 issue of JNCI containing “Why Do Phase III Clinical Trials in Oncology Fail so Often?”

120. Attached hereto as Appendix AMIRI02 is a true and correct copy of “Why Do Phase III Clinical Trials in Oncology Fail so Often?” as published in JNCI as held by the Penn State University Library. This PDF was secured from the

library's collection. In comparing Exhibit 2044 to Appendix AMIRI02, it is my determination that Exhibit 2044 is a true and correct copy of "Why Do Phase III Clinical Trials in Oncology Fail so Often?" by Laleh Amiri-Kordestani as published in JNCI.

121. The 008 field of the MARC record in Appendix AMIRI01 indicates the date of record creation. The 008 field of Appendix AMIRI01 indicates the Penn State University Library first acquired JNCI as of September 30, 1999 and held the journal in perpetuity until the publication of "Why Do Phase III Clinical Trials in Oncology Fail so Often?" Considering this information, it is my determination that JNCI April 18, 2012 and therefore "Why Do Phase III Clinical Trials in Oncology Fail so Often?" was made available to the public shortly after its initial publication as of April 18, 2012.

FF. Booth (Ex. 2045)

122. I have reviewed Exhibit 2045, "Oncology's Trials" by Bruce Booth as published in Nature Reviews Drug Discovery August 2003.

123. Attached hereto as Appendix BOOTH01 is a true and correct copy of the MARC record for Nature Reviews Drug Discovery as held by the Penn State University Library. I secured this record myself from the library's public catalog. The MARC record contained within Appendix BOOTH01 accurately describes the title, publisher and ISSN number of Nature Reviews Drug Discovery. The Showing

Results field present on page 3 of this record indicates the library's collection includes the August 2003 issue of Nature Reviews Drug Discovery containing "Oncology's Trials."

124. Attached hereto as Appendix BOOTH02 is a true and correct copy of "Oncology's Trials" as published in Nature Reviews Drug Discovery as held by the Penn State University Library. This PDF was secured from the library's collection. In comparing Exhibit 2045 to Appendix BOOTH02, it is my determination that Exhibit 2045 is a true and correct copy of "Oncology's Trials" by Bruce Booth as published in Nature Reviews Drug Discovery.

125. The 008 field of the MARC record in Appendix BOOTH01 indicates the date of record creation. The 008 field of Appendix BOOTH01 indicates the Penn State University Library first acquired Nature Reviews Drug Discovery as of February 21, 2002 and held the journal in perpetuity until the publication of "Oncology's Trials." Considering this information, it is my determination that Nature Reviews Drug Discovery August 2003 and therefore "Oncology's Trials" was made available to the public shortly after its initial publication in August 2003.

GG. Vasile (Ex. 2046)

126. I have reviewed Exhibit 2046, "Neoadjuvant Modified Folfoxiri in Locally Advanced Pancreatic Cancer by E. Vasile, et al. as published in Annals of Oncology September 2012.

127. Attached hereto as Appendix VASILE01 is a true and correct copy of “Neoadjuvant Modified Folfoxiri in Locally Advanced Pancreatic Cancer” as published in Annals of Oncology as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2046 to Appendix VASILE01, it is my determination that Exhibit 2046 is a true and correct copy of “Neoadjuvant Modified Folfoxiri in Locally Advanced Pancreatic Cancer” by E. Vasile, et al. as published in Annals of Oncology.

128. The 008 field of the MARC record in Appendix AO01 indicates the date of record creation. The 008 field of Appendix AO01 indicates the Penn State University Library first acquired Annals of Oncology as of June 16, 1999 and held the journal in perpetuity until the publication of “Neoadjuvant Modified Folfoxiri in Locally Advanced Pancreatic Cancer.” Considering this information, it is my determination that Annals of Oncology September 2012 and therefore “Neoadjuvant Modified Folfoxiri in Locally Advanced Pancreatic Cancer” was made available to the public shortly after its initial publication in September 2012.

HH. James (Ex. 2047)

129. I have reviewed Exhibit 2047, “Interim Analysis of a Phase II Study of Dose-modified FOLFIRINOX (mFOLFIRINOX) in Locally Advanced (LAPC) and Metastatic Pancreatic Cancer (MPC)” by Edward Samuel James, et al as published in Journal of Clinical Oncology January 20, 2014.

130. Attached hereto as Appendix JCO01 is a true and correct copy of the MARC record for Journal of Clinical Oncology as held by the University of Toronto Library. I secured this record myself from the library's public catalog. The MARC record contained within Appendix JCO01 accurately describes the title, publisher and ISSN number of Journal of Clinical Oncology. The View Online field present on page 2 of this record indicates the library's collection includes the January 20, 2014 issue of Journal of Clinical Oncology containing "Interim Analysis of a Phase II Study of Dose-modified FOLFIRINOX (mFOLFIRINOX) in Locally Advanced (LAPC) and Metastatic Pancreatic Cancer (MPC)."

131. Attached hereto as Appendix JAMES01 is a true and correct copy of "Interim Analysis of a Phase II Study of Dose-modified FOLFIRINOX (mFOLFIRINOX) in Locally Advanced (LAPC) and Metastatic Pancreatic Cancer (MPC)" as published in Journal of Clinical Oncology as held by the University of Toronto Library. This PDF was secured from the library's collection. In comparing Exhibit 2047 to Appendix JAMES01, it is my determination that Exhibit 2047 is a true and correct copy of "Interim Analysis of a Phase II Study of Dose-modified FOLFIRINOX (mFOLFIRINOX) in Locally Advanced (LAPC) and Metastatic Pancreatic Cancer (MPC)" by Edward Samuel James, et al as published in Journal of Clinical Oncology.

132. The 008 field of the MARC record in Appendix JCO01 indicates the date of record creation. The 008 field of Appendix JCO01 indicates the University of Toronto Library first acquired Journal of Clinical Oncology as of December 10, 1999 and held the journal in perpetuity until the publication of “Interim Analysis of a Phase II Study of Dose-modified FOLFIRINOX (mFOLFIRINOX) in Locally Advanced (LAPC) and Metastatic Pancreatic Cancer (MPC).” Considering this information, it is my determination that Journal of Clinical Oncology January 20, 2014 and therefore “Interim Analysis of a Phase II Study of Dose-modified FOLFIRINOX (mFOLFIRINOX) in Locally Advanced (LAPC) and Metastatic Pancreatic Cancer (MPC)” was made available to the public shortly after its initial publication as of January 20, 2014.

II. Stein (Ex. 2048)

133. I have reviewed Exhibit 2048, “Final Analysis of a Phase II Study of Modified FOLFIRINOX in Locally Advanced and Metastatic Pancreatic Cancer” by Stacey M Stein, et al. as published in British Journal of Cancer March 29, 2016.

134. Attached hereto as Appendix BJC01 is a true and correct copy of the MARC record for British Journal of Cancer as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix BJC01 accurately describes the title, publisher and ISSN number of British Journal of Cancer. The Showing Results field present

on page 3 of this record indicates the library's collection includes the March 29, 2016 issue of British Journal of Cancer containing "Final Analysis of a Phase II Study of Modified FOLFIRINOX in Locally Advanced and Metastatic Pancreatic Cancer."

135. Attached hereto as Appendix STEIN01 is a true and correct copy of "Final Analysis of a Phase II Study of Modified FOLFIRINOX in Locally Advanced and Metastatic Pancreatic Cancer" as published in British Journal of Cancer as held by the Penn State University Library. This PDF was secured from the library's collection. In comparing Exhibit 2048 to Appendix STEIN01, it is my determination that Exhibit 2048 is a true and correct copy of "Final Analysis of a Phase II Study of Modified FOLFIRINOX in Locally Advanced and Metastatic Pancreatic Cancer" by Stacey M Stein, et al. as published in British Journal of Cancer.

136. The 008 field of the MARC record in Appendix BJC01 indicates the date of record creation. The 008 field of Appendix BJC01 indicates the Penn State University Library first acquired British Journal of Cancer as of June 12, 2000 and held the journal in perpetuity until the publication of "Final Analysis of a Phase II Study of Modified FOLFIRINOX in Locally Advanced and Metastatic Pancreatic Cancer." Considering this information, it is my determination that British Journal of Cancer March 29, 2016 and therefore "Final Analysis of a Phase II Study of Modified FOLFIRINOX in Locally Advanced and Metastatic Pancreatic Cancer"

was made available to the public shortly after its initial publication as of March 29, 2016.

JJ. Yoshida (Ex. 2049)

137. I have reviewed Exhibit 2049, “A Multicenter Prospective Phase II Study of First-line Modified FOLFIRINOX for Unresectable Advanced Pancreatic Cancer” by Kensaku Yoshida, et al. as published in Oncotarget November 2017.

138. Attached hereto as Appendix ONCOTARGET01 is a true and correct copy of the MARC record for Oncotarget as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix ONCOTARGET01 accurately describes the title, publisher and ISSN number of Oncotarget. The Showing Results field present on page 3 of this record indicates the library's collection includes the November 2017 issue of Oncotarget containing “A Multicenter Prospective Phase II Study of First-line Modified FOLFIRINOX for Unresectable Advanced Pancreatic Cancer.”

139. Attached hereto as Appendix YOSHIDA01 is a true and correct copy of “A Multicenter Prospective Phase II Study of First-line Modified FOLFIRINOX for Unresectable Advanced Pancreatic Cancer” as published in Oncotarget as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2049 to Appendix YOSHIDA01, it is my determination that Exhibit 2049 is a true and correct copy of “A Multicenter

Prospective Phase II Study of First-line Modified FOLFIRINOX for Unresectable Advanced Pancreatic Cancer” by Kensaku Yoshida, et al. as published in Oncotarget.

140. The 008 field of the MARC record in Appendix ONCOTARGET01 indicates the date of record creation. The 008 field of Appendix ONCOTARGET01 indicates the Penn State University Library first acquired Oncotarget as of June 24, 2009 and held the journal in perpetuity until the publication of “A Multicenter Prospective Phase II Study of First-line Modified FOLFIRINOX for Unresectable Advanced Pancreatic Cancer.” Considering this information, it is my determination that Oncotarget November 2017 and therefore “A Multicenter Prospective Phase II Study of First-line Modified FOLFIRINOX for Unresectable Advanced Pancreatic Cancer” was made available to the public shortly after its initial publication in November 2017.

KK. Li (Ex. 2050)

141. I have reviewed Exhibit 2050, “Modified-FOLFIRINOX in Metastatic Pancreatic Cancer: A Prospective Study in Chinese Population” by Xiang Li, et al. as published in Cancer Letters October 10, 2017.

142. Attached hereto as Appendix LI01 is a true and correct copy of the MARC record for Cancer Letters as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record

contained within Appendix LI01 accurately describes the title, publisher and ISSN number of Cancer Letters. The Showing Results field present on page 3 of this record indicates the library's collection includes the October 10, 2017 issue of Cancer Letters containing "Modified-FOLFIRINOX in Metastatic Pancreatic Cancer: A Prospective Study in Chinese Population."

143. Attached hereto as Appendix LI02 is a true and correct copy of "Modified-FOLFIRINOX in Metastatic Pancreatic Cancer: A Prospective Study in Chinese Population" as published in Cancer Letters as held by the Penn State University Library. This PDF was secured from the library's collection. In comparing Exhibit 2050 to Appendix LI02, it is my determination that Exhibit 2050 is a true and correct copy of "Modified-FOLFIRINOX in Metastatic Pancreatic Cancer: A Prospective Study in Chinese Population" by Xiang Li, et al. as published in Cancer Letters.

144. The 008 field of the MARC record in Appendix LI01 indicates the date of record creation. The 008 field of Appendix LI01 indicates the Penn State University Library first acquired Cancer Letters as of February 23, 1998 and held the journal in perpetuity until the publication of "Modified-FOLFIRINOX in Metastatic Pancreatic Cancer: A Prospective Study in Chinese Population." Considering this information, it is my determination that Cancer Letters October 10, 2017 and therefore "Modified-FOLFIRINOX in Metastatic Pancreatic Cancer: A

Prospective Study in Chinese Population” was made available to the public shortly after its initial publication as of October 10, 2017.

LL. Ozaka (Ex. 2051)

145. I have reviewed Exhibit 2051, “A Phase II Study of Modified FOLFIRINOX for Chemotherapy-Naïve Patients with Metastatic Pancreatic Cancer” by Masato Ozaka, et al. as published in Cancer Chemotherapy and Pharmacology June 2018.

146. Attached hereto as Appendix OZAKA01 is a true and correct copy of the MARC record for Cancer Chemotherapy and Pharmacology as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix OZAKA01 accurately describes the title, publisher and ISSN number of Cancer Chemotherapy and Pharmacology. The Showing Results field present on page 3 of this record indicates the library's collection includes the June 2018 issue of Cancer Chemotherapy and Pharmacology containing “A Phase II Study of Modified FOLFIRINOX for Chemotherapy-Naïve Patients with Metastatic Pancreatic Cancer.”

147. Attached hereto as Appendix OZAKA02 is a true and correct copy of “A Phase II Study of Modified FOLFIRINOX for Chemotherapy-Naïve Patients with Metastatic Pancreatic Cancer” as published in Cancer Chemotherapy and Pharmacology as held by the Penn State University Library. This PDF was secured

from the library's collection. In comparing Exhibit 2051 to Appendix OZAKA02, it is my determination that Exhibit 2051 is a true and correct copy of "A Phase II Study of Modified FOLFIRINOX for Chemotherapy-Naïve Patients with Metastatic Pancreatic Cancer" by Masato Ozaka, et al. as published in Cancer Chemotherapy and Pharmacology.

148. The 008 field of the MARC record in Appendix OZAKA01 indicates the date of record creation. The 008 field of Appendix OZAKA01 indicates the Penn State University Library first acquired Cancer Chemotherapy and Pharmacology as of November 18, 1999 and held the journal in perpetuity until the publication of "A Phase II Study of Modified FOLFIRINOX for Chemotherapy-Naïve Patients with Metastatic Pancreatic Cancer." Considering this information, it is my determination that Cancer Chemotherapy and Pharmacology June 2018 and therefore "A Phase II Study of Modified FOLFIRINOX for Chemotherapy-Naïve Patients with Metastatic Pancreatic Cancer" was made available to the public shortly after its initial publication in June 2018.

MM. Wang (Ex. 2052)

149. I have reviewed Exhibit 2052, "The Efficacy and Safety of Modified FOLFIRINOX as First-Line Chemotherapy for Chinese Patients with Metastatic Pancreatic Cancer" by Zhi-Qiang Wang, et al. as published in Cancer Communications May 8, 2019.

150. Attached hereto as Appendix WANG01 is a true and correct copy of the MARC record for Cancer Communications as held by the Penn State University Library. I secured this record myself from the library's public catalog. The MARC record contained within Appendix WANG01 accurately describes the title, publisher and ISSN number of Cancer Communications. The Showing Results field present on page 3 of this record indicates the library's collection includes the May 8, 2019 issue of Cancer Communications containing "The Efficacy and Safety of Modified FOLFIRINOX as First-Line Chemotherapy for Chinese Patients with Metastatic Pancreatic Cancer."

151. Attached hereto as Appendix WANG02 is a true and correct copy of "The Efficacy and Safety of Modified FOLFIRINOX as First-Line Chemotherapy for Chinese Patients with Metastatic Pancreatic Cancer" as published in Cancer Communications as held by the Penn State University Library. This PDF was secured from the library's collection. In comparing Exhibit 2052 to Appendix WANG02, it is my determination that Exhibit 2052 is a true and correct copy of "The Efficacy and Safety of Modified FOLFIRINOX as First-Line Chemotherapy for Chinese Patients with Metastatic Pancreatic Cancer" by Zhi-Qiang Wang, et al. as published in Cancer Communications.

152. The 008 field of the MARC record in Appendix WANG01 indicates the date of record creation. The 008 field of Appendix WANG01 indicates the Penn

State University Library first acquired Cancer Communications as of March 23, 2018 and held the journal in perpetuity until the publication of “The Efficacy and Safety of Modified FOLFIRINOX as First-Line Chemotherapy for Chinese Patients with Metastatic Pancreatic Cancer.” Considering this information, it is my determination that Cancer Communications May 8, 2019 and therefore “The Efficacy and Safety of Modified FOLFIRINOX as First-Line Chemotherapy for Chinese Patients with Metastatic Pancreatic Cancer” was made available to the public shortly after its initial publication as of May 8, 2019.

NN. Ramanathan (Ex. 2053)

153. I have reviewed Exhibit 2053, “Phase IB/II Randomized Study of FOLFIRINOX Plus Pegylated Recombinant Human Hyaluronidase Versus FOLFIRINOX Alone in Patients With Metastatic Pancreatic Adenocarcinoma: SWOG S1313” by Ramesh K. Ramanathan, et al as published in Journal of Clinical Oncology May 1, 2019.

154. Attached hereto as Appendix JCO01 is a true and correct copy of the MARC record for Journal of Clinical Oncology as held by the University of Toronto Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix JCO01 accurately describes the title, publisher and ISSN number of Journal of Clinical Oncology. The View Online field present on page 2 of this record indicates the library's collection includes the May 1, 2019

issue of Journal of Clinical Oncology containing “Phase IB/II Randomized Study of FOLFIRINOX Plus Pegylated Recombinant Human Hyaluronidase Versus FOLFIRINOX Alone in Patients With Metastatic Pancreatic Adenocarcinoma: SWOG S1313.”

155. Attached hereto as Appendix RAMANATHAN01 is a true and correct copy of “Phase IB/II Randomized Study of FOLFIRINOX Plus Pegylated Recombinant Human Hyaluronidase Versus FOLFIRINOX Alone in Patients With Metastatic Pancreatic Adenocarcinoma: SWOG S1313” as published in Journal of Clinical Oncology as held by the University of Toronto Library. This PDF was secured from the library’s collection. In comparing Exhibit 2053 to Appendix RAMANATHAN01, it is my determination that Exhibit 2053 is a true and correct copy of “Phase IB/II Randomized Study of FOLFIRINOX Plus Pegylated Recombinant Human Hyaluronidase Versus FOLFIRINOX Alone in Patients With Metastatic Pancreatic Adenocarcinoma: SWOG S1313” by Ramesh K. Ramanathan, et al. as published in Journal of Clinical Oncology.

156. The 008 field of the MARC record in Appendix JCO01 indicates the date of record creation. The 008 field of Appendix JCO01 indicates the University of Toronto Library first acquired Journal of Clinical Oncology as of December 10, 1999 and held the journal in perpetuity until the publication of “Phase IB/II Randomized Study of FOLFIRINOX Plus Pegylated Recombinant Human

Hyaluronidase Versus FOLFIRINOX Alone in Patients With Metastatic Pancreatic Adenocarcinoma: SWOG S1313.” Considering this information, it is my determination that Journal of Clinical Oncology May 1, 2019 and therefore “Phase IB/II Randomized Study of FOLFIRINOX Plus Pegylated Recombinant Human Hyaluronidase Versus FOLFIRINOX Alone in Patients With Metastatic Pancreatic Adenocarcinoma: SWOG S1313” was made available to the public shortly after its initial publication as of May 1, 2019.

OO. Wei (Ex. 2054)

157. I have reviewed Exhibit 2054, “Monitoring Tumor Burden in Response to FOLFIRINOX Chemotherapy Via Profiling Circulating Cell-Free DNA in Pancreatic Cancer” by Tao Wei, et al. as published in Molecular Cancer Therapeutics January 2019.

158. Attached hereto as Appendix WEI01 is a true and correct copy of the MARC record for Molecular Cancer Therapeutics as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix WEI01 accurately describes the title, publisher and ISSN number of Molecular Cancer Therapeutics. The Showing Results field present on page 3 of this record indicates the library's collection includes the January 2019 issue of Molecular Cancer Therapeutics containing

“Monitoring Tumor Burden in Response to FOLFIRINOX Chemotherapy Via Profiling Circulating Cell-Free DNA in Pancreatic Cancer.”

159. Attached hereto as Appendix WEI02 is a true and correct copy of “Monitoring Tumor Burden in Response to FOLFIRINOX Chemotherapy Via Profiling Circulating Cell-Free DNA in Pancreatic Cancer” as published in Molecular Cancer Therapeutics as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2054 to Appendix WEI02, it is my determination that Exhibit 2054 is a true and correct copy of “Monitoring Tumor Burden in Response to FOLFIRINOX Chemotherapy Via Profiling Circulating Cell-Free DNA in Pancreatic Cancer” by Tao Wei, et al. as published in Molecular Cancer Therapeutics.

160. The 008 field of the MARC record in Appendix WEI01 indicates the date of record creation. The 008 field of Appendix WEI01 indicates the Penn State University Library first acquired Molecular Cancer Therapeutics as of February 12, 2002 and held the journal in perpetuity until the publication of “Monitoring Tumor Burden in Response to FOLFIRINOX Chemotherapy Via Profiling Circulating Cell-Free DNA in Pancreatic Cancer.” Considering this information, it is my determination that Molecular Cancer Therapeutics January 2019 and therefore “Monitoring Tumor Burden in Response to FOLFIRINOX Chemotherapy Via

Profiling Circulating Cell-Free DNA in Pancreatic Cancer” was made available to the public shortly after its initial publication in January 2019.

PP. Vivaldi 2019 (Ex. 2055)

161. I have reviewed Exhibit 2055, “Early Tumor Shrinkage and Depth of Response Evaluation in Metastatic Pancreatic Cancer Treated with First Line Chemotherapy: An Observational Retrospective Cohort Study” by Caterina Vivaldi, et al. as published in Cancers July 4, 2019.

162. Attached hereto as Appendix Cancers01 is a true and correct copy of the MARC record for Cancers as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix Cancers01 accurately describes the title, publisher and ISSN number of Cancers. The Showing Results field present on page 3 of this record indicates the library's collection includes the July 4, 2019 issue of Cancers containing “Early Tumor Shrinkage and Depth of Response Evaluation in Metastatic Pancreatic Cancer Treated with First Line Chemotherapy: An Observational Retrospective Cohort Study.”

163. Attached hereto as Appendix VIVALDI01 is a true and correct copy of “Early Tumor Shrinkage and Depth of Response Evaluation in Metastatic Pancreatic Cancer Treated with First Line Chemotherapy: An Observational Retrospective Cohort Study” as published in Cancers as held by the Penn State University Library.

This PDF was secured from the library's collection. In comparing Exhibit 2055 to Appendix VIVALDI01, it is my determination that Exhibit 2055 is a true and correct copy of "Early Tumor Shrinkage and Depth of Response Evaluation in Metastatic Pancreatic Cancer Treated with First Line Chemotherapy: An Observational Retrospective Cohort Study" by Caterina Vivaldi, et al. as published in Cancers.

164. The 008 field of the MARC record in Appendix CANCERS01 indicates the date of record creation. The 008 field of Appendix CANCERS01 indicates the Penn State University Library first acquired Cancers as of March 26, 2010 and held the journal in perpetuity until the publication of "Early Tumor Shrinkage and Depth of Response Evaluation in Metastatic Pancreatic Cancer Treated with First Line Chemotherapy: An Observational Retrospective Cohort Study." Considering this information, it is my determination that Cancers July 4, 2019 and therefore "Early Tumor Shrinkage and Depth of Response Evaluation in Metastatic Pancreatic Cancer Treated with First Line Chemotherapy: An Observational Retrospective Cohort Study" was made available to the public shortly after its initial publication as of July 4, 2019.

QQ. Peddi (Ex. 2056)

165. I have reviewed Exhibit 2056, "Multi-Institutional Experience with FOLFIRINOX in Pancreatic Adenocarcinoma" by Parvin F. Peddi, et al. as published in Journal of the Pancreas September 2012.

166. Attached hereto as Appendix PEDDI01 is a true and correct copy of the MARC record for Journal of the Pancreas as held by the Penn State University Library. I secured this record myself from the library's public catalog. The MARC record contained within Appendix PEDDI01 accurately describes the title, publisher and ISSN number of Journal of the Pancreas. The Showing Results field present on page 3 of this record indicates the library's collection includes the September 2012 issue of Journal of the Pancreas containing "Multi-Institutional Experience with FOLFIRINOX in Pancreatic Adenocarcinoma."

167. Attached hereto as Appendix PEDDI02 is a true and correct copy of "Multi-Institutional Experience with FOLFIRINOX in Pancreatic Adenocarcinoma" as published in Journal of the Pancreas as held by the Penn State University Library. This PDF was secured from the library's collection. In comparing Exhibit 2056 to Appendix PEDDI02, it is my determination that Exhibit 2056 is a true and correct copy of "Multi-Institutional Experience with FOLFIRINOX in Pancreatic Adenocarcinoma" by Parvin F. Peddi, et al. as published in Journal of the Pancreas.

168. The 008 field of the MARC record in Appendix PEDDI01 indicates the date of record creation. The 008 field of Appendix PEDDI01 indicates the Penn State University Library first acquired Journal of the Pancreas as of March 29, 2001 and held the journal in perpetuity until the publication of "Multi-Institutional Experience with FOLFIRINOX in Pancreatic Adenocarcinoma." Considering this

information, it is my determination that Journal of the Pancreas September 2012 and therefore “Multi-Institutional Experience with FOLFIRINOX in Pancreatic Adenocarcinoma” was made available to the public shortly after its initial publication in September 2012.

RR. Lowrey (Ex. 2057)

169. I have reviewed Exhibit 2057, “Activity of Front-line FOLFIRINOX (FFX) in Stage III/IV Pancreatic Adenocarcinoma (PC) at Memorial Sloan-Kettering Cancer Center (MSKCC)” by Maeve A. Lowery, et al as published in Journal of Clinical Oncology May 20, 2012.

170. Attached hereto as Appendix JCO01 is a true and correct copy of the MARC record for Journal of Clinical Oncology as held by the University of Toronto Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix JCO01 accurately describes the title, publisher and ISSN number of Journal of Clinical Oncology. The View Online field present on page 2 of this record indicates the library's collection includes the May 20, 2012 issue of Journal of Clinical Oncology containing “Activity of Front-line FOLFIRINOX (FFX) in Stage III/IV Pancreatic Adenocarcinoma (PC) at Memorial Sloan-Kettering Cancer Center (MSKCC).”

171. Attached hereto as Appendix LOWERY01 is a true and correct copy of “Activity of Front-line FOLFIRINOX (FFX) in Stage III/IV Pancreatic

Adenocarcinoma (PC) at Memorial Sloan-Kettering Cancer Center (MSKCC)” as published in Journal of Clinical Oncology as held by the University of Toronto Library. This PDF was from the library’s collection. In comparing Exhibit 2057 to Appendix LOWERY01, it is my determination that Exhibit 2057 is a true and correct copy of “Activity of Front-line FOLFIRINOX (FFX) in Stage III/IV Pancreatic Adenocarcinoma (PC) at Memorial Sloan-Kettering Cancer Center (MSKCC)” by Maeve A. Lowery, et al as published in Journal of Clinical Oncology.

172. The 008 field of the MARC record in Appendix JCO01 indicates the date of record creation. The 008 field of Appendix JCO01 indicates the University of Toronto Library first acquired Journal of Clinical Oncology as of December 10, 1999 and held the journal in perpetuity until the publication of “Activity of Front-line FOLFIRINOX (FFX) in Stage III/IV Pancreatic Adenocarcinoma (PC) at Memorial Sloan-Kettering Cancer Center (MSKCC).” Considering this information, it is my determination that Journal of Clinical Oncology May 20, 2012 and therefore “Activity of Front-line FOLFIRINOX (FFX) in Stage III/IV Pancreatic Adenocarcinoma (PC) at Memorial Sloan-Kettering Cancer Center (MSKCC)” was made available to the public shortly after its initial publication as of May 20, 2012.

SS. Hosein (Ex. 2058)

173. I have reviewed Exhibit 2058, “A Retrospective Study of Neoadjuvant FOLFIRINOX in Unresectable or Borderline-Resectable Locally Advanced

Pancreatic Adenocarcinoma” by Peter J. Hosein, et al. as published in BMC Cancer May 19, 2012.

174. Attached hereto as Appendix HOSEIN01 is a true and correct copy of the MARC record for BMC Cancer as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix HOSEIN01 accurately describes the title, publisher and ISSN number of BMC Cancer. The Showing Results field present on page 3 of this record indicates the library’s collection includes the May 19, 2012 issue of BMC Cancer containing “A Retrospective Study of Neoadjuvant FOLFIRINOX in Unresectable or Borderline-Resectable Locally Advanced Pancreatic Adenocarcinoma.”

175. Attached hereto as Appendix HOSEIN02 is a true and correct copy of “A Retrospective Study of Neoadjuvant FOLFIRINOX in Unresectable or Borderline-Resectable Locally Advanced Pancreatic Adenocarcinoma” as published in BMC Cancer as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2058 to Appendix HOSEIN02, it is my determination that Exhibit 2058 is a true and correct copy of “A Retrospective Study of Neoadjuvant FOLFIRINOX in Unresectable or Borderline-Resectable Locally Advanced Pancreatic Adenocarcinoma” by Peter J. Hosein, et al. as published in BMC Cancer.

176. The 008 field of the MARC record in Appendix HOSEIN01 indicates the date of record creation. The 008 field of Appendix HOSEIN01 indicates the Penn State University Library first acquired BMC Cancer as of February 12, 2001 and held the journal in perpetuity until the publication of “A Retrospective Study of Neoadjuvant FOLFIRINOX in Unresectable or Borderline-Resectable Locally Advanced Pancreatic Adenocarcinoma.” Considering this information, it is my determination that BMC Cancer May 19, 2012 and therefore “A Retrospective Study of Neoadjuvant FOLFIRINOX in Unresectable or Borderline-Resectable Locally Advanced Pancreatic Adenocarcinoma” was made available to the public shortly after its initial publication as of May 19, 2012.

TT. Ghorani (Ex. 2059)

177. I have reviewed Exhibit 2059, “Safety and Efficacy of Modified FOLFIRINOX for Advanced Pancreatic Adenocarcinoma: A UK Single-Centre Experience” by Ehsan Ghorani, et al. as published in Oncology October 2015.

178. Attached hereto as Appendix GHORANI01 is a true and correct copy of the MARC record for Oncology as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix GHORANI01 accurately describes the title, publisher and ISSN number of Oncology. The Showing Results field present on page 3 of this record indicates the library's collection includes the October 2015 issue of Oncology

containing “Safety and Efficacy of Modified FOLFIRINOX for Advanced Pancreatic Adenocarcinoma: A UK Single-Centre Experience.”

179. Attached hereto as Appendix GHORANI02 is a true and correct copy of “Safety and Efficacy of Modified FOLFIRINOX for Advanced Pancreatic Adenocarcinoma: A UK Single-Centre Experience” as published in Oncology as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2059 to Appendix GHORANI02, it is my determination that Exhibit 2059 is a true and correct copy of “Safety and Efficacy of Modified FOLFIRINOX for Advanced Pancreatic Adenocarcinoma: A UK Single-Centre Experience” by Ehsan Ghorani, et al. as published in Oncology.

180. The 008 field of the MARC record in Appendix GHORANI01 indicates the date of record creation. The 008 field of Appendix GHORANI01 indicates the Penn State University Library first acquired Oncology as of January 25, 2000 and held the journal in perpetuity until the publication of “Safety and Efficacy of Modified FOLFIRINOX for Advanced Pancreatic Adenocarcinoma: A UK Single-Centre Experience.” Considering this information, it is my determination that Oncology October 2015 and therefore “Safety and Efficacy of Modified FOLFIRINOX for Advanced Pancreatic Adenocarcinoma: A UK Single-Centre Experience” was made available to the public shortly after its initial publication in October 2015.

UU. Kaga (Ex. 2060)

181. I have reviewed Exhibit 2060, “Early Tumor Shrinkage as a Predictor of Favorable Outcomes in Patients with Advanced Pancreatic Cancer Treated with FOLFIRINOX” by Yasuhiro Kaga, et al. as published in Oncotarget October 2016.

182. Attached hereto as Appendix ONCOTARGET01 is a true and correct copy of the MARC record for Oncotarget as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix ONCOTARGET01 accurately describes the title, publisher and ISSN number of Oncotarget. The Showing Results field present on page 3 of this record indicates the library's collection includes the October 2016 issue of Oncotarget containing “Early Tumor Shrinkage as a Predictor of Favorable Outcomes in Patients with Advanced Pancreatic Cancer Treated with FOLFIRINOX.”

183. Attached hereto as Appendix KAGA01 is a true and correct copy of “Early Tumor Shrinkage as a Predictor of Favorable Outcomes in Patients with Advanced Pancreatic Cancer Treated with FOLFIRINOX” as published in Oncotarget as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2060 to Appendix KAGA01, it is my determination that Exhibit 2060 is a true and correct copy of “Early Tumor Shrinkage as a Predictor of Favorable Outcomes in Patients with Advanced

Pancreatic Cancer Treated with FOLFIRINOX” by Yasuhiro Kaga, et al. as published in Oncotarget.

184. The 008 field of the MARC record in Appendix ONCOTARGET01 indicates the date of record creation. The 008 field of Appendix ONCOTARGET01 indicates the Penn State University Library first acquired Oncotarget as of June 24, 2009 and held the journal in perpetuity until the publication of “Early Tumor Shrinkage as a Predictor of Favorable Outcomes in Patients with Advanced Pancreatic Cancer Treated with FOLFIRINOX.” Considering this information, it is my determination that Oncotarget October 2016 and therefore “Early Tumor Shrinkage as a Predictor of Favorable Outcomes in Patients with Advanced Pancreatic Cancer Treated with FOLFIRINOX” was made available to the public shortly after its initial publication in October 2016.

VV. De Jesus (Ex. 2061)

185. I have reviewed Exhibit 2061, “Retrospective Comparison of the Efficacy and the Toxicity of Standard and Modified FOLFIRINOX Regimens in Patients with Metastatic Pancreatic Adenocarcinoma” by Victor Hugo Fonseca de Jesus as published in Journal of Gastrointestinal Oncology August 2018.

186. Attached hereto as Appendix FONSECA01 is a true and correct copy of the MARC record for Journal of Gastrointestinal Oncology as held by the Penn State University Library. I secured this record myself from the library’s public

catalog. The MARC record contained within Appendix FONSECA01 accurately describes the title, publisher and ISSN number of Journal of Gastrointestinal Oncology. The Showing Results field present on page 3 of this record indicates the library's collection includes the August 2018 issue of Journal of Gastrointestinal Oncology containing “Retrospective Comparison of the Efficacy and the Toxicity of Standard and Modified FOLFIRINOX Regimens in Patients with Metastatic Pancreatic Adenocarcinoma.”

187. Attached hereto as Appendix FONSECA02 is a true and correct copy of “Retrospective Comparison of the Efficacy and the Toxicity of Standard and Modified FOLFIRINOX Regimens in Patients with Metastatic Pancreatic Adenocarcinoma” as published in Journal of Gastrointestinal Oncology as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2061 to Appendix FONSECA02, it is my determination that Exhibit 2061 is a true and correct copy of “Retrospective Comparison of the Efficacy and the Toxicity of Standard and Modified FOLFIRINOX Regimens in Patients with Metastatic Pancreatic Adenocarcinoma” by Victor Hugo Fonseca de Jesus as published in Journal of Gastrointestinal Oncology.

188. The 008 field of the MARC record in Appendix FONSECA01 indicates the date of record creation. The 008 field of Appendix FONSECA01 indicates the

Penn State University Library first acquired Journal of Gastrointestinal Oncology as of April 1, 2011 and held the journal in perpetuity until the publication of “Retrospective Comparison of the Efficacy and the Toxicity of Standard and Modified FOLFIRINOX Regimens in Patients with Metastatic Pancreatic Adenocarcinoma.” Considering this information, it is my determination that Journal of Gastrointestinal Oncology August 2018 and therefore “Retrospective Comparison of the Efficacy and the Toxicity of Standard and Modified FOLFIRINOX Regimens in Patients with Metastatic Pancreatic Adenocarcinoma” was made available to the public shortly after its initial publication in August 2018.

WW. Kang (Ex. 2062)

189. I have reviewed Exhibit 2062, “Comparison of Efficacy and Safety between Standard-dose and Modified-dose FOLFIRINOX as a First-line Treatment of Pancreatic Cancer” by Huapyeong Kang, et al. as published in World Journal of Gastrointestinal Oncology November 15, 2018.

190. Attached hereto as Appendix KANG01 is a true and correct copy of the MARC record for World Journal of Gastrointestinal Oncology as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix KANG01 accurately describes the title, publisher and ISSN number of World Journal of Gastrointestinal Oncology. The Showing Results field present on page 3 of this record indicates the

library's collection includes the November 15, 2018 issue of World Journal of Gastrointestinal Oncology containing “Comparison of Efficacy and Safety between Standard-dose and Modified-dose FOLFIRINOX as a First-line Treatment of Pancreatic Cancer.”

191. Attached hereto as Appendix KANG02 is a true and correct copy of “Comparison of Efficacy and Safety between Standard-dose and Modified-dose FOLFIRINOX as a First-line Treatment of Pancreatic Cancer” as published in World Journal of Gastrointestinal Oncology as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2062 to Appendix KANG02, it is my determination that Exhibit 2062 is a true and correct copy of “Comparison of Efficacy and Safety between Standard-dose and Modified-dose FOLFIRINOX as a First-line Treatment of Pancreatic Cancer” by Huapyeong Kang, et al. as published in World Journal of Gastrointestinal Oncology.

192. The 008 field of the MARC record in Appendix KANG01 indicates the date of record creation. The 008 field of Appendix KANG01 indicates the Penn State University Library first acquired World Journal of Gastrointestinal Oncology as of October 16, 2003 and held the journal in perpetuity until the publication of “Comparison of Efficacy and Safety between Standard-dose and Modified-dose FOLFIRINOX as a First-line Treatment of Pancreatic Cancer.” Considering this information, it is my determination that World Journal of Gastrointestinal Oncology

November 15, 2018 and therefore “Comparison of Efficacy and Safety between Standard-dose and Modified-dose FOLFIRINOX as a First-line Treatment of Pancreatic Cancer” was made available to the public shortly after its initial publication as of November 15, 2018.

XX. Yamada (Ex. 2063)

193. I have reviewed Exhibit 2063, “Severe Neutropenia is Associated with Better Clinical Outcomes in Patients with Advanced Pancreatic Cancer Who Receive Modified FOLFIRINOX Therapy” by Yunami Yamada, et al. as published in Cancers November 16, 2018.

194. Attached hereto as Appendix Cancers01 is a true and correct copy of the MARC record for Cancers as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix Cancers01 accurately describes the title, publisher and ISSN number of Cancers. The Showing Results field present on page 3 of this record indicates the library's collection includes the November 16, 2018 issue of Cancers containing “Severe Neutropenia is Associated with Better Clinical Outcomes in Patients with Advanced Pancreatic Cancer Who Receive Modified FOLFIRINOX Therapy.”

195. Attached hereto as Appendix YAMADA01 is a true and correct copy of “Severe Neutropenia is Associated with Better Clinical Outcomes in Patients with

Advanced Pancreatic Cancer Who Receive Modified FOLFIRINOX Therapy” as published in Cancers as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2063 to Appendix YAMADA01, it is my determination that Exhibit 2063 is a true and correct copy of “Severe Neutropenia is Associated with Better Clinical Outcomes in Patients with Advanced Pancreatic Cancer Who Receive Modified FOLFIRINOX Therapy” by Yunami Yamada, et al. as published in Cancers.

196. The 008 field of the MARC record in Appendix CANCERS01 indicates the date of record creation. The 008 field of Appendix CANCERS01 indicates the Penn State University Library first acquired Cancers as of March 26, 2010 and held the journal in perpetuity until the publication of “Severe Neutropenia is Associated with Better Clinical Outcomes in Patients with Advanced Pancreatic Cancer Who Receive Modified FOLFIRINOX Therapy.” Considering this information, it is my determination that Cancers November 16, 2018 and therefore “Severe Neutropenia is Associated with Better Clinical Outcomes in Patients with Advanced Pancreatic Cancer Who Receive Modified FOLFIRINOX Therapy” was made available to the public shortly after its initial publication as of November 16, 2018.

YY. Eraslan (Ex. 2064)

197. I have reviewed Exhibit 2064, “First Line Modified Folfirinox versus Gemcitabine for Advanced Pancreatic Cancer: A Single Institution Retrospective

Experience” by Emrah Eraslan, et al as published in Journal of Oncological Science April 2019.

198. Attached hereto as Appendix ERASLAN01 is a true and correct copy of the MARC record for Journal of Oncological Science as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix ERASLAN01 accurately describes the title, publisher and ISSN number of Journal of Oncological Science. The Showing Results field present on page 3 of this record indicates the library’s collection includes the April 2019 issue of Journal of Oncological Science containing “First Line Modified Folfirinox versus Gemcitabine for Advanced Pancreatic Cancer: A Single Institution Retrospective Experience.”

199. Attached hereto as Appendix ERASLAN02 is a true and correct copy of “First Line Modified Folfirinox versus Gemcitabine for Advanced Pancreatic Cancer: A Single Institution Retrospective Experience” as published in Journal of Oncological Science as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2064 to Appendix ERASLAN02, it is my determination that Exhibit 2064 is a true and correct copy of “First Line Modified Folfirinox versus Gemcitabine for Advanced Pancreatic Cancer: A Single Institution Retrospective Experience” by Emrah Eraslan, et al as published in Journal of Oncological Science.

200. The 008 field of the MARC record in Appendix ERASLAN01 indicates the date of record creation. The 008 field of Appendix ERASLAN01 indicates the Penn State University Library first acquired Journal of Oncological Science as of January 10, 2017 and held the journal in perpetuity until the publication of “First Line Modified Folfirinox versus Gemcitabine for Advanced Pancreatic Cancer: A Single Institution Retrospective Experience.” Considering this information, it is my determination that Journal of Oncological Science April 2019 and therefore “First Line Modified Folfirinox versus Gemcitabine for Advanced Pancreatic Cancer: A Single Institution Retrospective Experience” was made available to the public shortly after its initial publication in April 2019.

ZZ. Sasaki (Ex. 2065)

201. I have reviewed Exhibit 2065, “Improvement of Treatment Outcomes for Metastatic Pancreatic Cancer: A Real-world Data Analysis” by Takashi Sasaki, et al. as published in In Vivo January 2019.

202. Attached hereto as Appendix SASAKI01 is a true and correct copy of the MARC record for In Vivo as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix SASAKI01 accurately describes the title, publisher and ISSN number of In Vivo. The Showing Results field present on page 3 of this record indicates the library's collection includes the January 2019 issue of In Vivo

containing “Improvement of Treatment Outcomes for Metastatic Pancreatic Cancer: A Real-world Data Analysis.”

203. Attached hereto as Appendix SASAKI02 is a true and correct copy of “Improvement of Treatment Outcomes for Metastatic Pancreatic Cancer: A Real-world Data Analysis” as published in In Vivo as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2065 to Appendix SASAKI02, it is my determination that Exhibit 2065 is a true and correct copy of “Improvement of Treatment Outcomes for Metastatic Pancreatic Cancer: A Real-world Data Analysis” by Takashi Sasaki, et al. as published in In Vivo.

204. The 008 field of the MARC record in Appendix SASAKI01 indicates the date of record creation. The 008 field of Appendix SASAKI01 indicates the Penn State University Library first acquired In Vivo as of April 23, 2009 and held the journal in perpetuity until the publication of “Improvement of Treatment Outcomes for Metastatic Pancreatic Cancer: A Real-world Data Analysis.” Considering this information, it is my determination that In Vivo January 2019 and therefore “Improvement of Treatment Outcomes for Metastatic Pancreatic Cancer: A Real-world Data Analysis” was made available to the public shortly after its initial publication in January 2019.

AAA. Vivaldi 2021 (Ex. 2066)

205. I have reviewed Exhibit 2066, “Comprehensive Pharmacogenetic Analysis of DPYD, UGT, CDA, and ABCB1 Polymorphisms in Pancreatic Cancer Patients Receiving mFOLFIRINOX or Gemcitabine plus Nab-paclitaxel” by Caterina Vivaldi, et al. as published in The Pharmacogenics Journal April 2021.

206. Attached hereto as Appendix VIVALDI02 is a true and correct copy of the MARC record for The Pharmacogenics Journal as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix VIVALDI02 accurately describes the title, publisher and ISSN number of The Pharmacogenics Journal. The Showing Results field present on page 3 of this record indicates the library’s collection includes the April 2021 issue of The Pharmacogenics Journal containing “Comprehensive Pharmacogenetic Analysis of DPYD, UGT, CDA, and ABCB1 Polymorphisms in Pancreatic Cancer Patients Receiving mFOLFIRINOX or Gemcitabine plus Nab-paclitaxel.”

207. Attached hereto as Appendix VIVALDI03 is a true and correct copy of “Comprehensive Pharmacogenetic Analysis of DPYD, UGT, CDA, and ABCB1 Polymorphisms in Pancreatic Cancer Patients Receiving mFOLFIRINOX or Gemcitabine plus Nab-paclitaxel” as published in The Pharmacogenics Journal as held by the Penn State University Library. This PDF was secured from the library’s

collection. In comparing Exhibit 2066 to Appendix VIVALDI03, it is my determination that Exhibit 2066 is a true and correct copy of “Comprehensive Pharmacogenetic Analysis of DPYD, UGT, CDA, and ABCB1 Polymorphisms in Pancreatic Cancer Patients Receiving mFOLFIRINOX or Gemcitabine plus Nab-paclitaxel” by Caterina Vivaldi, et al. as published in The Pharmacogenics Journal.

208. The 008 field of the MARC record in Appendix VIVALDI02 indicates the date of record creation. The 008 field of Appendix VIVALDI02 indicates the Penn State University Library first acquired The Pharmacogenics Journal as of June 10, 2002 and held the journal in perpetuity until the publication of “Comprehensive Pharmacogenetic Analysis of DPYD, UGT, CDA, and ABCB1 Polymorphisms in Pancreatic Cancer Patients Receiving mFOLFIRINOX or Gemcitabine plus Nab-paclitaxel.” Considering this information, it is my determination that The Pharmacogenics Journal April 2021 and therefore “Comprehensive Pharmacogenetic Analysis of DPYD, UGT, CDA, and ABCB1 Polymorphisms in Pancreatic Cancer Patients Receiving mFOLFIRINOX or Gemcitabine plus Nab-paclitaxel” was made available to the public shortly after its initial publication in April 2021.

BBB. Cavanna (Ex. 2067)

209. I have reviewed Exhibit 2067, “Modified FOLFIRINOX for Unresectable Locally Advanced/Metastatic Pancreatic Cancer: A Real-world

Comparison of an Attenuated with a Full Dose in a Single Center Experience” by Luigi Cavanna, et al. as published in Oncotargets & Therapy April 2019.

210. Attached hereto as Appendix CAVANNA01 is a true and correct copy of the MARC record for Oncotargets & Therapy as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix CAVANNA01 accurately describes the title, publisher and ISSN number of Oncotargets & Therapy. The Showing Results field present on page 3 of this record indicates the library's collection includes the April 2019 issue of Oncotargets & Therapy containing “Modified FOLFIRINOX for Unresectable Locally Advanced/Metastatic Pancreatic Cancer: A Real-world Comparison of an Attenuated with a Full Dose in a Single Center Experience.”

211. Attached hereto as Appendix CAVANNA02 is a true and correct copy of “Modified FOLFIRINOX for Unresectable Locally Advanced/Metastatic Pancreatic Cancer: A Real-world Comparison of an Attenuated with a Full Dose in a Single Center Experience” as published in Oncotargets & Therapy as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2067 to Appendix CAVANNA02, it is my determination that Exhibit 2067 is a true and correct copy of “Modified FOLFIRINOX for Unresectable Locally Advanced/Metastatic Pancreatic Cancer: A Real-world Comparison of an

Attenuated with a Full Dose in a Single Center Experience” by Luigi Cavanna, et al. as published in Oncotargets & Therapy.

212. The 008 field of the MARC record in Appendix CAVANNA01 indicates the date of record creation. The 008 field of Appendix CAVANNA01 indicates the Penn State University Library first acquired Oncotargets & Therapy as of April 28, 2009 and held the journal in perpetuity until the publication of “Modified FOLFIRINOX for Unresectable Locally Advanced/Metastatic Pancreatic Cancer: A Real-world Comparison of an Attenuated with a Full Dose in a Single Center Experience.” Considering this information, it is my determination that Oncotargets & Therapy April 2019 and therefore “Modified FOLFIRINOX for Unresectable Locally Advanced/Metastatic Pancreatic Cancer: A Real-world Comparison of an Attenuated with a Full Dose in a Single Center Experience” was made available to the public shortly after its initial publication in April 2019.

CCC. Cui (Ex. 2068)

213. I have reviewed Exhibit 2068, “A Chinese Retrospective Multicenter Study of First-Line Chemotherapy for Advanced Pancreatic Cancer” by Hanzhi Cui as published in Medical Science Monitor October 26, 2020.

214. Attached hereto as Appendix CUI01 is a true and correct copy of the MARC record for Medical Science Monitor as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC

record contained within Appendix CUI01 accurately describes the title, publisher and ISSN number of Medical Science Monitor. The Showing Results field present on page 3 of this record indicates the library's collection includes the October 26, 2020 issue of Medical Science Monitor containing "A Chinese Retrospective Multicenter Study of First-Line Chemotherapy for Advanced Pancreatic Cancer."

215. Attached hereto as Appendix CUI02 is a true and correct copy of "A Chinese Retrospective Multicenter Study of First-Line Chemotherapy for Advanced Pancreatic Cancer" as published in Medical Science Monitor as held by the Penn State University Library. This PDF was secured from the library's collection. In comparing Exhibit 2068 to Appendix CUI02, it is my determination that Exhibit 2068 is a true and correct copy of "A Chinese Retrospective Multicenter Study of First-Line Chemotherapy for Advanced Pancreatic Cancer" by Hanzhi Cui as published in Medical Science Monitor.

216. The 008 field of the MARC record in Appendix CUI01 indicates the date of record creation. The 008 field of Appendix CUI01 indicates the Penn State University Library first acquired Medical Science Monitor as of June 17, 2002 and held the journal in perpetuity until the publication of "A Chinese Retrospective Multicenter Study of First-Line Chemotherapy for Advanced Pancreatic Cancer." Considering this information, it is my determination that Medical Science Monitor October 26, 2020 and therefore "A Chinese Retrospective Multicenter Study of

First-Line Chemotherapy for Advanced Pancreatic Cancer” was made available to the public shortly after its initial publication as of October 26, 2020.

DDD. Pacheco-Barcia (Ex. 2069)

217. I have reviewed Exhibit 2069, “A Systemic Inflammation Response Index (SIRI) Correlates with Survival and Predicts Oncological Outcome for mFOLFIRINOX Therapy in Metastatic Pancreatic Cancer” by Vilma Pacheco-Barcia, et al. as published in Pancreas March 2020.

218. Attached hereto as Appendix PANCREATOLOGY01 is a true and correct copy of the MARC record for Pancreas as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix PANCREATOLOGY01 accurately describes the title, publisher and ISSN number of Pancreas. The Showing Results field present on page 3 of this record indicates the library's collection includes the March 2020 issue of Pancreas containing “A Systemic Inflammation Response Index (SIRI) Correlates with Survival and Predicts Oncological Outcome for mFOLFIRINOX Therapy in Metastatic Pancreatic Cancer.”

219. Attached hereto as Appendix PACHECO01 is a true and correct copy of “A Systemic Inflammation Response Index (SIRI) Correlates with Survival and Predicts Oncological Outcome for mFOLFIRINOX Therapy in Metastatic Pancreatic Cancer” as published in Pancreas as held by the Penn State University

Library. This PDF was secured from the library's collection. In comparing Exhibit 2069 to Appendix PACHECO01, it is my determination that Exhibit 2069 is a true and correct copy of "A Systemic Inflammation Response Index (SIRI) Correlates with Survival and Predicts Oncological Outcome for mFOLFIRINOX Therapy in Metastatic Pancreatic Cancer" by Vilma Pacheco-Barcia, et al. as published in Pancreas.

220. The 008 field of the MARC record in Appendix PANCREATOLOGY01 indicates the date of record creation. The 008 field of Appendix PANCREATOLOGY01 indicates the Penn State University Library first acquired Pancreas as of June 20, 1986 and held the journal in perpetuity until the publication of "A Systemic Inflammation Response Index (SIRI) Correlates with Survival and Predicts Oncological Outcome for mFOLFIRINOX Therapy in Metastatic Pancreatic Cancer." Considering this information, it is my determination that Pancreas March 2020 and therefore "A Systemic Inflammation Response Index (SIRI) Correlates with Survival and Predicts Oncological Outcome for mFOLFIRINOX Therapy in Metastatic Pancreatic Cancer" was made available to the public shortly after its initial publication in March 2020.

EEE. Takeda (Ex. 2070)

221. I have reviewed Exhibit 2070, “Improved Prognosis of Pancreatic Cancer Patients with Peritoneal Metastasis” by Tsuyoshi Takeda, et al. as published in *Pancreas* August 2021.

222. Attached hereto as Appendix PANCREATOLOGY01 is a true and correct copy of the MARC record for *Pancreas* as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix PANCREATOLOGY01 accurately describes the title, publisher and ISSN number of *Pancreas*. The Showing Results field present on page 3 of this record indicates the library's collection includes the August 2021 issue of *Pancreas* containing “Improved Prognosis of Pancreatic Cancer Patients with Peritoneal Metastasis.”

223. Attached hereto as Appendix TAKEDA01 is a true and correct copy of “Improved Prognosis of Pancreatic Cancer Patients with Peritoneal Metastasis” as published in *Pancreas* as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2070 to Appendix TAKEDA01, it is my determination that Exhibit 2070 is a true and correct copy of “Improved Prognosis of Pancreatic Cancer Patients with Peritoneal Metastasis” by Tsuyoshi Takeda, et al. as published in *Pancreas*.

224. The 008 field of the MARC record in Appendix PANCREATOLOGY01 indicates the date of record creation. The 008 field of Appendix PANCREATOLOGY01 indicates the Penn State University Library first acquired Pancreas as of June 20, 1986 and held the journal in perpetuity until the publication of “Improved Prognosis of Pancreatic Cancer Patients with Peritoneal Metastasis.” Considering this information, it is my determination that Pancreas August 2021 and therefore “Improved Prognosis of Pancreatic Cancer Patients with Peritoneal Metastasis” was made available to the public shortly after its initial publication in August 2021.

FFF. Zhou (Ex. 2071)

225. I have reviewed Exhibit 2071, “Delta HU is a Potential Marker to Predict Chemotherapy Response for Unresectable Pancreatic Ductal Adenocarcinoma” by Yizhang Zhou, et al. as published in Pancreas June 2021.

226. Attached hereto as Appendix PANCREATOLOGY01 is a true and correct copy of the MARC record for Pancreas as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix PANCREATOLOGY01 accurately describes the title, publisher and ISSN number of Pancreas. The Showing Results field present on page 3 of this record indicates the library's collection includes the June 2021 issue

of Pancreas containing “Delta HU is a Potential Marker to Predict Chemotherapy Response for Unresectable Pancreatic Ductal Adenocarcinoma.”

227. Attached hereto as Appendix ZHOU01 is a true and correct copy of “Delta HU is a Potential Marker to Predict Chemotherapy Response for Unresectable Pancreatic Ductal Adenocarcinoma” as published in Pancreas as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2071 to Appendix ZHOU01, it is my determination that Exhibit 2071 is a true and correct copy of “Delta HU is a Potential Marker to Predict Chemotherapy Response for Unresectable Pancreatic Ductal Adenocarcinoma” by Yizhang Zhou, et al. as published in Pancreas.

228. The 008 field of the MARC record in Appendix PANCREATOLOGY01 indicates the date of record creation. The 008 field of Appendix PANCREATOLOGY01 indicates the Penn State University Library first acquired Pancreas as of June 20, 1986 and held the journal in perpetuity until the publication of “Delta HU is a Potential Marker to Predict Chemotherapy Response for Unresectable Pancreatic Ductal Adenocarcinoma.” Considering this information, it is my determination that Pancreas June 2021 and therefore “Delta HU is a Potential Marker to Predict Chemotherapy Response for Unresectable Pancreatic Ductal Adenocarcinoma” was made available to the public shortly after its initial publication in June 2021.

GGG. Oberstein (Ex. 2072)

229. I have reviewed Exhibit 2072, “Pancreatic Cancer: Why Is It So Hard to Treat?” by Paul E. Oberstein, et al as published in Therapeutic Advances in Gastroenterology July 2013.

230. Attached hereto as Appendix OBERSTEIN01 is a true and correct copy of the MARC record for Therapeutic Advances in Gastroenterology as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix OBERSTEIN01 accurately describes the title, publisher and ISSN number of Therapeutic Advances in Gastroenterology. The Showing Results field present on page 3 of this record indicates the library's collection includes the July 2013 issue of Therapeutic Advances in Gastroenterology containing “Pancreatic Cancer: Why Is It So Hard to Treat?.”

231. Attached hereto as Appendix OBERSTEIN02 is a true and correct copy of “Pancreatic Cancer: Why Is It So Hard to Treat?” as published in Therapeutic Advances in Gastroenterology as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 2072 to Appendix OBERSTEIN02, it is my determination that Exhibit 2072 is a true and correct copy of “Pancreatic Cancer: Why Is It So Hard to Treat?” by Paul E. Oberstein, et al as published in Therapeutic Advances in Gastroenterology.

232. The 008 field of the MARC record in Appendix OBERSTEIN01 indicates the date of record creation. The 008 field of Appendix OBERSTEIN01 indicates the Penn State University Library first acquired Therapeutic Advances in Gastroenterology as of August 28, 2008 and held the journal in perpetuity until the publication of “Pancreatic Cancer: Why Is It So Hard to Treat?.” Considering this information, it is my determination that Therapeutic Advances in Gastroenterology July 2013 and therefore “Pancreatic Cancer: Why Is It So Hard to Treat?” was made available to the public shortly after its initial publication in July 2013.

HHH. Knox (Ex. 2075)

233. I have reviewed Exhibit 2075, “PASS-01: Randomized Phase II Trial of Modified FOLFIRINOX Versus Gemcitabine/Nab-Paclitaxel and Molecular Correlatives for Previously Untreated Metastatic Pancreatic Cancer” by Jennifer J. Knox, et al. as published in Journal of Clinical Oncology September 10, 2025.

234. Attached hereto as Appendix JCO01 is a true and correct copy of the MARC record for Journal of Clinical Oncology as held by the University of Toronto Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix JCO01 accurately describes the title, publisher and ISSN number of Journal of Clinical Oncology. The View Online field present on page 2 of this record indicates the library's collection includes the June 5, 2024

issue of Journal of Clinical Oncology containing “Early Results of the PASS-01 Trial: Pancreatic Adenocarcinoma Signature Stratification for Treatment-01.”

235. Attached hereto as Appendix KNOX01 is a true and correct copy of “PASS-01: Randomized Phase II Trial of Modified FOLFIRINOX Versus Gemcitabine/Nab-Paclitaxel and Molecular Correlatives for Previously Untreated Metastatic Pancreatic Cancer” as published in Journal of Clinical Oncology as held by the University of Toronto Library. This PDF was secured from the library’s collection. In comparing Exhibit 2075 to Appendix KNOX01, it is my determination that Exhibit 2075 is a true and correct copy of “PASS-01: Randomized Phase II Trial of Modified FOLFIRINOX Versus Gemcitabine/Nab-Paclitaxel and Molecular Correlatives for Previously Untreated Metastatic Pancreatic Cancer” by Jennifer J. Knox, et al as published in Journal of Clinical Oncology.

236. The 008 field of the MARC record in Appendix JCO01 indicates the date of record creation. The 008 field of Appendix JCO01 indicates the University of Toronto Library first acquired Journal of Clinical Oncology as of December 10, 1999 and held the journal in perpetuity until the publication of “EaPASS-01: Randomized Phase II Trial of Modified FOLFIRINOX Versus Gemcitabine/Nab-Paclitaxel and Molecular Correlatives for Previously Untreated Metastatic Pancreatic Cancer.” Considering this information, it is my determination that Journal of Clinical Oncology September 10, 2025 and therefore “PASS-01:

Randomized Phase II Trial of Modified FOLFIRINOX Versus Gemcitabine/Nab-Paclitaxel and Molecular Correlatives for Previously Untreated Metastatic Pancreatic Cancer” was made available to the public shortly after its initial publication as of September 10, 2025.

I declare under penalty of perjury under the laws of the State of
Pennsylvania that the foregoing is true and correct to the best of my knowledge.

Executed on this 10th day of November, 2025.

A handwritten signature in black ink, appearing to read 'June Ann Munford', written over a horizontal line.

June Ann Munford, MILS

Appendix ALNAIM01



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MARC View

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003 SIRSI

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016 7 a| 2026590-6 2| DE-600

016 7 a| 012088579 2| Uk

019 a| DO NOT EDIT this 360 MARC RECORD

022 a| 1477-092X l| 1078-1552 y| 1078-1552

035 a| (WaSeSS)ssj0008728

040 a| F#A b| eng c| F#A d| OCLCQ d| MUQ d| NSD d| OCLCQ d| WAU d| ORE d| TXJ d| CO3 d| OCLCQ d| AGL d| OCLCF d| VT2 d| OCLCO d| Z5A d| OCLCO d| OCLCA d| U3W d| OCLCO d| EZC d| OCLCO d| DLC d| AU@ d| OCLCO d| WYU d| OCLCO d| UKMGB d| OCLCO d| OCLCA d| NJT d| OCLCO d| QGK d| OCLCO d| OCLCQ d| OCL d| UBY d| UAB d| OCLCL d| WaSeSS

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050 1 4 a| RC271.C5

060 0 0 a| W1 b| JO803D

070 0 a| RC271.C5 b| J68

082 0 4 a| 616.994061 1| https://id.oclc.org/worldcat/ddc/E3xHPFT4KgyfbFF6fKcRyx6WPM

130 0 a| Journal of oncology pharmacy practice (Online)

210 0 0 a| J Oncol Pharm Pract

210 0 0 a| J Oncol Pharm Practice

210 0 a| J. oncol. pharm. pract. b| (Online)

222 0 a| Journal of oncology pharmacy practice b| (Online)

245 1 0 a| Journal of oncology pharmacy practice h| [electronic resource].

260 3| -1999 : a| [Houndmills, Basingstoke, Hampshire, UK] : b| Stockton Press

260 2 3| 2000 : a| [New York?] : b| Nature America Inc.

260 2 3| 2001-Mar. 2006 : a| [London] : b| Edward Arnold

260 3 3| June 2006- : a| Los Angeles : b| Sage Publications

310 a| Eight issues a year, b| 2017-

321 a| Bimonthly, b| 2014-2016

321 a| Quarterly, b| 1995-2013

362 1 a| Print began with vol. 1, no. 1 (June 1995).

525 a| Includes occasional supplements.

530 a| Also issued in print.

538 a| Mode of access: World Wide Web.

550 a| Official publication of the International Society for Oncology Pharmacy Practitioners.

588 a| Description based on: Vol. 5, no. 1 (Mar. 1999); title from HTML contents (publishers website, viewed Oct. 25, 2010).

588 a| Latest issue consulted: Vol. 29, issue 3 (June 2023) (Sage, viewed June 21, 2023).

650 0 a| Cancer x| Chemotherapy v| Periodicals.

650 0 a| Clinical pharmacology v| Periodicals.

650 0 a| Oncology v| Periodicals.

650 0 a| Pharmacy v| Periodicals.

650 0 a| Oncology.

650 2 a| Medical Oncology

655 0 a| Electronic journals.

710 2 a| International Society of Oncology Pharmacy Practitioners. 1| https://id.oclc.org/worldcat/entity/E39QH7JmmTyHq8Mf6PJWc8qHRg.

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Appendix ALNAIM02

Therapeutic drug monitoring of cancer chemotherapy

Lamya Alnaim, PharmD

Therapeutic drug monitoring is not routinely used for chemotherapy agents. There are several reasons, but one major drawback is the lack of established therapeutic concentration ranges. Combination chemotherapy makes the establishment of therapeutic ranges for individual drugs difficult, the concentration-effect relationship for a single drug may not be the same as when that drug is used in a drug combination. Pharmacokinetic optimization protocols for many classes of cytotoxic compounds exist in specialized centers, and some of these protocols are now part of large multicentre trials. Nonetheless, TDM clearly has the potential to improve the clinical use of chemotherapy agents, most of which have very narrow therapeutic indices and highly variable pharmacokinetics. A substantial body of literature accumulating during the past 15 years demonstrates relationships between systemic exposure to various chemotherapy agents and their toxic or therapeutic effects. This article reviews TDM concepts in addition to tools based on pharmacokinetic modeling of chemotherapy agents. The administered dose of chemotherapy agents is sometimes adjusted individually using either a priori

or a posteriori methods. These models can only be applied by using the same dose and schedule as the original study. Bayesian estimation offers more flexibility in blood sampling times and, owing to its precision and to the amount of information provided is the method of choice for ensuring that a given patient benefits from the desired systemic exposure. Moreover, the role and application of Pharmacogenetics as a tool for individualizing chemotherapy is discussed highlighting the agents and mechanisms that have been well studied and defined and their relevance to clinical practice. Finally, this paper addresses issues critical to the optimal use of TDM in a clinical setting, and the role of clinical pharmacist in this regard. In addition, it discusses future developments in this field that can contribute to improving cancer chemotherapy in terms of patient outcome and survival. *J Oncol Pharm Practice* (2007) 13: 207–221.

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INTRODUCTION

Therapeutic drug monitoring (TDM) has been utilized in the clinical care of patients from the early 1960s. It involves the measurement and interpretation of drug concentrations in biological fluids

and the individualization of drug dosages or schedules to maximize therapeutic outcomes, minimize toxicities, or both.¹ In theory, a drug should fulfill several criteria in order for TDM to be valuable. These include presence of considerable inter- or intra-individual pharmacokinetic variability, existence of a defined relationship between concentration and pharmacological effects, a narrow therapeutic window, and the availability of a defined and accurate method for drug quantification in biological fluids.^{2,3} TDM is broadly applied to a diversity of drugs from

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different therapeutic classes, such as cardiovascular agents, antiepileptics, antibiotics, respiratory smooth muscle relaxants, and anti-inflammatory agents, some cancer chemotherapeutic agents, immunosuppressants, and antidepressants. In the midst of all these therapeutic classes, TDM has limited use with antineoplastic agents. Anticancer agents are generally characterized by a large inter-individual pharmacokinetic variability; relationships linking toxicity to systemic exposure, and toxic effects better related to exposure than to dose or dose intensity. Consequently, TDM can be and has been successfully applied to optimize anticancer treatments including carboplatin, methotrexate and 5-FU as well as etoposide, and 6-mercaptopurine.^{4,5-10}

LIMITATIONS OF TDM FOR CANCER CHEMOTHERAPY

The clinical value of TDM for antineoplastic agents is at this time restricted by several factors.¹¹⁻¹³ First, there exists an imperfect understanding of the pharmacology and pharmacokinetics of most antineoplastic agents. Second, the plasma drug concentration is an indirect measure of the amount of drug in the target tissue, because the site of action is frequently distant from intravascular spaces in addition to the fact that solid tumors may have their own unique blood supply. Third, there is naturally a long lag time between the measurement of drug in plasma and evaluation of the definitive pharmacodynamic effect, which is usually, cure. If improvement in cure rate is used as the outcome variable this usually requires at least 5 years of follow-up to dependably evaluate the outcome. Consequently, studies require more time and more complex process that is significantly different from that of studies for drugs with quicker effects, such as antibiotics. Fourth, the difficulty in identifying concentration-effect relationships because antineoplastic agents are almost always given in combination.¹⁴ Therefore, it would be very difficult to accurately define the pharmacodynamics of each individual agent. In addition, combination therapy also complicates the pharmacodynamics of drug toxicity.

Fifth, cancer is a group of heterogeneous diseases, with inherent characteristics that affect the concentration-effect relationship for antineoplastic agents. They display heterogeneity in blood supply and cellular characteristics, leading to different levels

of sensitivity and resistance to antineoplastic agents.¹⁵

Only few agents fulfill all the TDM prerequisites because of the lack of well-defined relationships between efficacy and systemic exposure. Such relationships have been demonstrated only for very few drug/disease couples, for example methotrexate and acute lymphoblastic leukemia (B lineage), carboplatin and ovarian cancer,¹⁶ and 5-FU and metastasis colorectal¹⁷ or head and neck cancer.^{18,19}

POTENTIAL BENEFIT OF TDM FOR CANCER CHEMOTHERAPY

Many clinical cancer trials show the benefits of maximum chemotherapy intensity¹⁴ signifying the need to treat patients with doses that will produce concentrations in the upper end of the nontoxic range to increase likelihood of response or cure. If toxic plasma concentrations can be defined for each agent, then TDM could be useful in identifying which agents are being overdosed or under dosed in any given regimen.

TDM in cancer chemotherapy has additional advantages besides individualizing chemotherapy to improve efficacy and avoid toxicity; these include enhancement of compliance, minimization of pharmacokinetic variability among patients, dose adjustment in patients with hepatic and (or) renal dysfunction,¹⁵ and detection of drug interactions.³

Despite the limitations facing TDM application for antineoplastic agents, there exists vast potential for advancement of cancer treatment if TDM can be appropriately practiced. Antineoplastic agents satisfy the criteria for TDM: vastly variable pharmacokinetics and narrow therapeutic indices. In addition, when treating patients with cancer disease, seeking the highest efficacy from chemotherapy is an important principle because of the magnitude of the consequences to cancer patients. Sub-optimal therapy can greatly reduce the probability of cure for curable cancers. On the other hand, side effects, such as myelosuppression, can be life-threatening and may be related to higher than optimal therapy. Consequently, a therapeutic range that defines efficacy concentrations as well as toxicity concentrations would have enormous clinical utility.

PHARMACOKINETICS AND PHARMACODYNAMICS OF CHEMOTHERAPY

Drug pharmacokinetics depends on the four basic processes namely—absorption, distribution, metabolism, and elimination. These processes differ between patients and result in substantial differences in plasma concentrations for the same dosage given to different patients. Moreover, variability can also be observed in pharmacokinetics as a result of day-to-day changes in an individual patient's ability to metabolize or excrete a drug. Intra-patient variability can be explained in-part by patient noncompliance, drug interactions, and in all cases will require tailoring dosages to fit the current needs of the specific patient.

The concentration of drug in plasma does not always reflect the concentrations at the cellular level, which is the site of action for most drugs; however, it is typically difficult or impossible to measure. Pharmacodynamics also exhibits wide inter- and intra-individual variability. In practice, plasma drug concentrations usually provide an accessible measurement for defining the pharmacokinetic parameters, such as systemic clearance, steady-state plasma concentration (C_{ps}), and area under the concentration-time curve (AUC).

THE CONCEPT OF DOSE-INTENSITY AND SYSTEMIC EXPOSURE

The concept of dose-intensity was first advocated by Hryniuk and Bush,²⁰ from breast cancer clinical trials data. Dose-intensity is defined as the amount of drug given per unit time (eg, mg/m² per week), and is based on the postulation that dose scheduling or infusion time does not directly determine tumor cell kill, which may not hold true for many antineoplastic agents. Furthermore, it grants equal importance to time delays and dose reductions.²¹ It is vital only for tumors responsive to the medications being evaluated, where the dose-response curves is often steep, and an increase in the dose or dose-intensity would lead to improved clinical effects.²²

The concept of systemic exposure has been studied as an alternative to dose-intensity for anticancer drugs.^{11,23} It is presented as a potentially more useful measurement of dose-intensity.¹¹ C_{ps} and AUC are PK parameters that can be used

to measure systemic exposure to a drug. For instance, in the treatment of osteosarcoma, where 4- or 6-h MTX infusions are usually administered, peak plasma concentration at the end of the infusion was shown to be linked to efficacy.^{24,25}

In case of drugs that metabolize to active intracellular metabolites, eg, mercaptopurine (MP) and MTX, concentrations of their active metabolites in surrogate cells (eg, erythrocytes) have also been used to measure systemic exposure.

Several different applications of systemic exposure have been used in cancer treatment. The European Organization for Research and Treatment of Cancer (EORTC) Pharmacokinetics and Metabolism Group proposed a guided dose increase in phase I clinical trials to assist determinations of the maximum tolerated dose (MTD) for investigational anticancer drugs.^{26,27} Soon after, a newer concept named the maximum tolerated systemic exposure (MTSE) was proposed as a move forward to MTD for phase I and II clinical trials of antineoplastic agents.^{28,29}

For a few schedule-dependent drugs such as etoposide, it has been found that more complex indices are more appropriate. Etoposide is a cell-cycle specific cytotoxic drug, that means that the cells have to be exposed to it during the sensitive part of the cell cycle (late S-phase) and exposure maintained for long enough to kill the cells. The therapeutic window is highly dependent on the duration of the infusion. Duration above a certain threshold concentration was found to be the best predictor of efficacy in small-cell lung cancer.⁸

Over the past 15 years, studies have been done to establish the association between systemic exposure and therapeutic outcomes. Many studies of pharmacodynamics of numerous cancer chemotherapeutic agents are performed and reviewed in greater detail elsewhere.^{13,30-35}

EVALUATION OF THE RESPONSE

The predicted response is more often toxicity than efficacy. Severity scales have been defined for some types of toxicity (eg mucositis and diarrhea), while quantitative measurements to evaluate hematological toxicity are available. Efficacy can be evaluated through a near-immediate response, such as tumor necrosis³⁶ or tumor activity (using sophisticated methods, such as positron emission tomography scan, or PET-scan) or through a long-term response,

such as time to progression, continuous time without relapse, or survival time. However, the latter data are much more difficult to obtain.

METHODS FOR DOSE INDIVIDUALIZATION AND TDM OF ANTICANCER AGENTS

The methods used for individual dose adjustment can be classified into three categories:

(I) *a priori* methods, (ii) test dose method, (iii) *A posteriori* methods.

(i) *A priori* methods

A priori methods allow the estimation of the dose necessary to reach a target exposure in a given patient using morphological, biological, and physiological data, such as body weight, age, gender, serum creatinine level, and glomerular filtration rate (GFR). The design of such a formula requires a close relationship between an estimated parameter and a pretreatment factor. The most frequently used formulae are those for carboplatin.³⁷⁻⁴³ Both Calvert's⁴¹ and Chatelut's⁴³ formulae have proved their applicability and their efficiency. With Calvert's formula, the dose necessary to achieve a target AUC (between 3 and 8 mg/mL) is calculated using the GFR. Chatelut's formula which was developed using pharmacokinetic modeling only requires age, gender, and weight and serum creatinine level and is particularly appropriate for outpatients. The impact of population pharmacokinetic modeling on *a priori* dose adjustment can also be illustrated by studies dealing with topotecan,^{42,43} which showed close relationships between topotecan clearance and renal function (serum creatinine or creatinine clearance), and body size. These population studies suggested *a priori* dose adjustments on the basis of these individual factors but, as they were not entirely validated, the relationships proposed deserve further prospective evaluation.

Even though *a priori* methods are simple to implement and somewhat balance for the inter-individual pharmacokinetic variability, their predictive performance is not as good as that of *a posteriori* methods.⁴⁴ Typical average bias and precision of <10 and 20%, respectively, can generally be expected with these methods.

(ii) The Test-dose Method

This method includes two steps: first, the individual pharmacokinetic parameters are determined after

administration of a bolus injection of a moderate dose using multiple blood samples; second, these parameters are used to calculate the full dose necessary to achieve the target exposure. The principle of this method is much debated because it can be used only when the pharmacokinetics are linear and always involves additional blood samples and a delay before efficient treatment is begun. This method is very often used for MTX as it requires dose adjustment most routinely because of its very large inter-individual pharmacokinetic variability (drug concentration as well as total clearance can vary over a 5-fold range from one patient to another after administration of a standard fixed dose).⁴⁵⁻⁴⁷

(iii) *A Posteriori* Methods

a. Nomograms

Nomograms have been routinely used for individual dose adjustment of fluorouracil (5-FU). The abscissas represent the observed AUC_{0-48h} values and the ordinate is the decrease (as a percentage) in dose needed to reach the full target AUC.

For example, Santini *et al.*¹² developed such an approach: they measured AUC in the middle of a 5-day infusion and then proposed to adjust the dose of 5-FU in order to maintain the full AUC, which is reached at the end of the infusion, under the toxic threshold. The benefit of 5-FU dose adjustment with a similar method in patients with head and neck carcinoma has been well demonstrated in a trial comparing it with a standard fixed dose.⁴⁸ The response rate was similar in the two arms while the mean administered dose and toxicity were reduced in the nomogram arm.

b. Multilinear regression (MLR) Methods

Multilinear regression models aim to evaluate one exposure variable (mainly AUC) using very few (generally two or three) blood samples collected at particular times. Exposure is often described as a linear function of the concentrations measured at particular time-points.

MLR is not based on a pharmacokinetic model and the equation results only from correlations (and cross correlations) between certain sampling times and the exposure index studied. Such methods have been proposed to monitor the AUCs of a few drugs and metabolites, for instance etoposide, doxorubicin, carboplatin, cyclophosphamide, topotecan, irinotecan, and metabolites.⁴⁹⁻⁵⁸ However, as far as anti-cancer drugs are concerned, these methods are generally not regarded as sufficiently precise for TDM. Additionally, they are hardly compatible with routine clinical practice because of the requirements

for intense blood sampling which is not appropriate for routine clinical care.

c. Maximum *a posteriori* (MAP) Bayesian methods
Maximum *a posteriori* Bayesian estimation methods require a pharmacokinetic population model and a few concentration data collected after or during administration of the drug. In addition, physiological or biological figures are also used in the calculation. In the past, the two-stage approach was the method most often used in oncology to describe population pharmacokinetics. The first stage is the estimation of each patient's pharmacokinetic parameter values, using nonlinear regression or maximum likelihood estimation and a full concentration profile. In the second stage, the mean and standard deviation of each parameter, as well as the correlation and covariance of each parameter with the others, are calculated. This modeling method is simple but requires multiple blood samples from each patient and leads to overestimation of the inter-individual as well as the residual variability.

In contrast, the one-stage method is true population modeling. The data observed in all patients are considered as a whole, so that it is possible to scatter the different sampling times amongst several patients, to the point that each patient can even undergo only one blood sampling. The most frequently used method is called the non-linear mixed-effect model. It is a parametric method. Inter-individual pharmacokinetic variability can sometime be partly explained by individual factors or covariates that may be very easy to obtain, such as age, gender, or weight. Thus, this population approach provides information on which covariates are important in determining the pharmacokinetics of the drug and how much variability can be explained by them. This method mixes fixed effects (such as doses, covariables, and population parameters, taking eventually into account the effects of covariables on concentrations) and random effects (ie the intra-individual variability and the unexplained part of the inter-individual variability). Non-linear mixed-effect modeling is increasingly used for one-stage pharmacokinetic as well as pharmacodynamic population modeling. The most powerful and generally employed program using this approach is NONMEM.⁵⁹ In the non-parametric methods,^{60,61} the population pharmacokinetic parameters are not constrained to some assumed distribution but are described by the observed distribution itself. Consequently, these methods are able to discover, with no external help, unsuspected subpopulations

which could be missed using parametric techniques. NPEM⁶²⁻⁶⁴ is the only program using this approach that has been employed in oncology.

MAP Bayesian estimation has been used for TDM for 30 years. This strategy takes into account the pharmacokinetic characteristics of a typical population, in a statistical form on the one hand, and fractional data collected in the studied patient, such as one or two plasma drug concentrations and body weight on the other.

MAP Bayesian methods have major advantages over other strategies, as they allow:

- (i) Visual checking of modeling efficiency, by looking at the concordance between the measured concentrations and the predicted concentration-time curve.
- (ii) Estimation of several pharmacokinetic parameter values and exposure indices simultaneously.
- (iii) Flexibility with respect to the sampling times rendering this method more relevant to real life and the constraints of a clinical department.
- (iv) Inclusion of new data in the population database allows progressive refinement of the population pharmacokinetic model.

The main drawback is that such an estimator is difficult to develop, but it is easy to use. Bayesian estimators were developed for a large number of anticancer drugs: methotrexate,⁶⁵⁻⁶⁸ carboplatin,⁶⁹⁻⁷² cisplatin,⁷³ etoposide,^{74,75} teniposide,⁷⁶ anthracyclines (doxorubicin and pirarubicin),⁷⁷⁻⁷⁹ irinotecan,^{80,81} topotecan,^{43,82} vincristine,⁸³ vinorelbine,^{84,85} and suramin.^{86, 87}

Generally two or three blood samples were enough to predict individual pharmacokinetic parameter values with low bias and good precision. Few of these estimators have been used, whether in controlled exposure clinical trials or in routine practice, for example for monitoring methotrexate,⁶⁵ carboplatin,⁶⁹⁻⁷² and suramin.^{86,87} Bayesian estimation allowed doses, and sometimes the administration schedule, to be accurately adjusted. Moreover, good control of toxicity and very few major toxic events (despite a frequent increase in the mean administered doses compared with fixed standard doses) were generally reported.

The implementation of TDM in clinical practice can be illustrated with the examples of many anticancer drugs. MTX is still the drug for which plasma

concentration monitoring is the most routinely used, with two distinctive aims: (I) MTX TDM;⁶⁶ (ii) individual dose adjustment of folinic rescue.⁶⁷ Bayesian adaptive control strategies have been successfully used to adjust MTX dose in real time during 24-h as well as 8-h infusions. In the comparative trial by Evans *et al.*,¹¹ MTX clearance was estimated on the basis of plasma concentrations 1 and 6 h after the start of the infusion, and the dose was eventually adjusted at 8 h to achieve the target range exposure. Pignon *et al.*⁶⁸ used dose adjustment at 6 h, using samples collected at 4 and 5 h, to reach concentrations of 5×10^{-4} or 10^{-3} M at the end of an 8-h infusion. Another study performed in children who received 24-h MTX infusions,⁶⁵ Bayesian forecasting was employed to adjust the dose of folinic acid, used as an antidote. A single blood sample (collected at 48 h) was shown to be sufficient to predict the time at which the MTX concentration reached a predefined threshold below which the administration of folinic acid could be stopped (ie 0.2 mol/L).

Chatelut *et al.*¹⁴ reported successful dose adjustment of carboplatin in adults with germ cell tumors. Each patient received a 1-h infusion each day for 4 days. The first dose was calculated using the *a priori* Chatelut's formula⁴⁰ in order to reach a daily AUC of 5 mg/min/mL, and was sometimes modulated according to the patient's status. The interdose AUC was observed on days 1 and 2 and the dose was readjusted using Bayesian estimation on days 3 and 4, in order to obtain a total AUC of 20 mg/min/mL. The Bayesian estimator used was based on a population model obtained using NONMEM and took into account body surface area, body weight, age, serum creatinine level, gender, and two serum concentrations corresponding to samples collected about 1 and 4 h after the end of infusion. The results were very good as all patients effectively received a total AUC very close to the target value. The first clinical interest of this TDM method for such intensified chemotherapies was a good control of toxicity.

Nguyen *et al.* attempted to use a population analysis for the identification of patient covariates that might appreciably influence vinorelbine disposition and also tried to define a limited sampling strategy for further Bayesian estimation of individual pharmacokinetic parameters. The population pharmacokinetic model was built in a sequential manner on a subset of two-thirds of the data, starting with a covariate-free model then progressing to a covariate model using the nonlinear-mixed effect methodology. The remaining one-third of the data was used to validate several sparse sampling designs. It was found

that a linear three-compartment model characterized vinorelbine blood concentrations. Two primary pharmacokinetic parameters [total clearance (CL) and volume of distribution (Vd) were related to various combinations of covariates. The relationship for total clearance was dependent on the patient's body surface area (BSA), weight (Wt), serum creatinine (Cr_s), and platelet count before administration (Plt). The optimal limited sampling strategy consisted of a combination of three measured blood concentrations; the first immediately before the end of infusion or 20 min later, the second at either 1, 3, or 6 h and the third at 24 h after drug administration.^{88,89}

Urien and Lokiec investigated the pharmacokinetics of unbound and total plasma platinum using a population approach in order to identify patient characteristics that may influence the disposition of the cisplatin. Pharmacokinetic and demographic data were collected from adult patients treated with 30-min daily infusions of cisplatin for various malignancies. Unbound and total platinum concentration-time data were analyzed using a nonlinear mixed effects model. A linear two-compartment model best described total and unbound platinum plasma concentration-time data. Unbound clearance was dependent on BSA and creatinine clearance, and Vd was dependent on BSA. The pharmacokinetic parameter, $f(m)/V(m)$, a measure of the clearance of unbound platinum due to irreversible plasma binding, was related to serum protein concentration and to the inverse of dose per $m(2)$. The covariate modeling of CL, Vd(1), and $f(m)/V(m)$ improved the inter-subject variabilities associated with these parameters. The final pharmacokinetic models were validated using 200 bootstrap samples from the original datasets.⁹⁰

On the other hand, de Jongh *et al.* characterized cisplatin population pharmacokinetics in adult cancer patients by a one-compartment linear model with BSA as the only significant covariate that impacted on both CL and Vd with the use of NONMEM, performing generalized-additive modeling to identify candidate covariates.⁹¹

Kellie *et al.* reported the results of their work which was done to investigate the pharmacokinetics of docetaxel (40 mg/m² week using sparse concentration-time data collected from patients with advanced cancer and studying the relationships between docetaxel clearance and 21 covariates. They followed a population pharmacokinetic approach to analyze plasma concentration-time data and the mean population and individual *posterior* Bayesian estimates of docetaxel clearance were estimated

using P-PHARM. Significant relationships were found between clearance and $1/t_{\max}$ and several of the liver function enzymes. This model provided both precise and unbiased predictions of docetaxel concentrations in a validation group of patients and an estimate of the population mean.⁹²

Earlier work by Launay-Iliadis *et al.*, which was two population analyses on short i.v. infusion of docetaxel, one using nonlinear mixed-effect modeling (NONMEM) and the other using nonparametric maximum-likelihood (NPML) sequentially to determine the structural model; estimate the mean population parameters, including clearance (Cl) and inter-individual variability; and find influences of demographic covariates on them. They found that a three-compartment model gave the best fit to the data and the final NONMEM regression model for expressed Cl (in liters per hour) directly as a function of BSA.⁹³

EVALUATION OF THE IMPACT OF THERAPEUTIC DRUG MONITORING

Numerous studies have evaluated the effect of individual dose adjustment by studying the percentage of patients who achieved a target exposure, which may support the performance of the pharmacokinetic parameter value forecasting, but is not sufficient to demonstrate the relevance of TDM. Relevance of adaptive control methods has to be studied from a clinical point of view because physicians need to 'treat the patient and not the concentration'.⁹⁴ Individual dose optimization is based on relationships between systemic drug exposure and therapeutic end-points (tumor response, toxicity, and survival), which helps to define a target range of exposure, but the benefit of adaptive administration has to be evaluated prospectively. Two exciting approaches have been used in oncology: a direct and a more indirect one. The direct approach studied the impact of TDM on patient outcomes and, in randomized trials, compared treatment responses (such as survival at a given time, relapse rates, frequency, and severity of toxic events) after individualized dose adjustment and after administration of standard fixed doses.^{95,96} This approach can be difficult to implement and requires large groups of patients and often a long follow-up.

A more recently proposed indirect approach used a pharmacodynamic model to predict the time course of leucopenia from the drug concentration versus

time curve.^{97,98} Such models are a true justification of TDM when they concern clinical end-points such as leucopenia, which is a primary toxicity of many anticancer drugs and is difficult to predict. Contrary to the direct approach, which relates to a specific treatment or schedule, such models could be used with different drugs or schedules. These two approaches are based on the individual pharmacokinetic parameter estimates, so a sparse sampling strategy might render them more readily applicable in clinical practice.

PHARMACOGENETICS

Pharmacogenetics is the science of incorporating information on inherited genetic variability into predicting treatment response. It provides information that allows the clinician to make a determination of appropriateness and risk of drug therapy prior to the initiation of therapy. It also may then have an additional place in selecting drug or dosage alterations during the treatment for a disease process.

A better understanding of pharmacogenetic associations is especially important in cancer chemotherapy, as many chemotherapeutic agents given for cancer are characterized by a narrow therapeutic index.⁹⁹

Polymorphisms in both the individual's genome, as well as the tumor genome, will affect drug response. Drug-related toxicity almost exclusively depends on the genotype of non-tumor tissue. So, inherited polymorphisms will have a key role with respect to toxicity, a crucial dose-limiting factor in most cancer chemotherapy regimens.

Pharmacogenetics aims to use knowledge of these variations to 'tailor' therapy for improved response and reduced toxicity. Most research so far has focused on single polymorphisms. A more comprehensive approach to predict treatment response will be to consider genetic variation in entire biological and pharmacological pathways.

Genetic variations are the result of multiple mechanisms such as single nucleotide polymorphisms (SNPs) (over 90%), insertion, deletion, tandem repeats, and microsatellites. In an attempt to individualize therapy, pharmacogenetics is used in search for answers to the hereditary basis for individual differences in drug response.

Some drugs require metabolism to be activated or inactivated. Some enzymes involved in the biotransformation have polymorphic expression. Therefore,

assessing enzyme activity (ie phenotype) or gene mutations (ie genotype) could help to predict optimal dose regimens.⁹⁹⁻¹⁰¹

Fluorouracil (5-FU) is the most frequent chemotherapy drug used in combination therapy to treat a wide variety of malignancies of the gastrointestinal tract, breast, and head and neck. Eighty to ninety percent of 5-FU dose is catabolized into inactive dihydrofluorouracil (5FUH2) by dihydropyrimidine dehydrogenase (DPD). A genetic polymorphism caused by mutations in the DPD gene results in DPD enzyme with partial to absolute loss of activity. Patients who are genetically deficient in this enzyme are at particular risk of life-threatening toxicity.¹⁰² The gene for DPD has recently been localized to chromosome 1p22, and at least one mutation has been identified.¹⁰³⁻¹⁰⁵ The most frequent mutation in patients with partial or complete DPD deficiency is allele DPD*2A. Patients heterozygous for this polymorphism have low DPD activity and toxicity to 5FU. Family studies in pediatric patients with DPD-deficiency phenotypes and in cancer patients having moderate to severe toxicity after 5-FU treatment show poor genotype-phenotype concordance. It seems that genotyping tests for DPD mutations have low sensitivity in identifying high-risk patients, and as yet no single test has been validated as a tool to individualize 5-FU therapy. Currently, the apparently high false-negative rate for DPD as a predictor for severe 5-FU toxicity restricts the testing of DPD*2A.

On the other hand, the thymidylate-synthase promoter-enhancer region (TSER) polymorphism has been investigated in studies that evaluate response or toxicity from 5-FU treatment. Overall, findings indicate that genotypes that are associated with lower thymidylate-synthase expression confer an increased sensitivity towards 5-FU therapy, although possibly at the expense of greater toxicity. However, most of these studies had limited sample sizes, which needs to be taken into consideration when interpreting the results.¹⁰⁶

Mercaptopurine (MP) is widely used in combination with methotrexate for childhood acute lymphoblastic leukemia (ALL) and in the treatment of Hodgkin disease. As an inactive prodrug, MP must be converted to its active intracellular nucleotide metabolites to exert cytotoxicity. To this point, intracellular thioguanine nucleotides (TGN) serve as the most helpful measure of systemic exposure. Thiopurine S-methyltransferase (TPMT) is a cytosolic enzyme that catalyzes the S-methylation of MP, an inactivation pathway that competes with the activation pathway to TGNs.

Pharmacogenetics causes variability in the metabolism of MP.¹⁰⁷ A polymorphic variation exists in the activity of this enzyme¹⁰⁷⁻¹⁰⁹ with 10% of the population having intermediate activity and 1 in 300 individuals inheriting TPMT deficiency as an autosomal recessive trait. Deficiency in TPMT, owing to homozygosity for low TPMT can lead to marked hematopoietic toxicity if treated with routine doses of MP. TPMT activity varies widely in the subpopulation with intermediate TPMT activity and can be related inversely to formation of the TGN metabolites and therapeutic response. Finally, homozygotes for high TPMT activity may be resistant to MP therapy and can tolerate high doses of the drug, without experiencing myelosuppression because they force more of the drug to the inactivation pathway and less to TGN.

Individualization of MP dose, based on TPMT activity, is a good example of the use of pharmacogenetics to optimize drug therapy. Patients who are TPMT-deficient can be safely and effectively treated with MP if their dosage is reduced. Thus, TPMT is an example of a clinically significant genetic polymorphism where prospective genotyping might allow individualization of drug therapy and thereby maximize efficacy and minimize toxicity. TPMT genotyping or phenotyping is now being used in major centers for dose optimization, in order to reduce the likelihood of adverse drug reaction in children with acute lymphocytic leukemia.¹¹⁰

Many anticancer drugs are extensively metabolized by CYP enzymes, especially the isoenzymes CYP3A4 and CYP2C8. The UDP glycosyltransferases (UGTs) represent a superfamily of enzymes that catalyze addition of the glycosyl group from a nucleotide sugar to a hydrophobic molecule.

Irinotecan, is an anticancer agent used in the treatment of colon cancer, lung, and other solid tumors. Irinotecan is activated by a carboxylesterase to form the active metabolite SN-38, a potent inhibitor of topoisomerase I. SN-38 is further conjugated by UGT specifically the UGT 1A1 isoform.^{111,112} This same isoform conjugates bilirubin or several endogenous substrates. UGT1A1 promoter polymorphisms result in reduced UGT1A1 expression and activity. Reduced UGT1A1 is linked to a high risk (about 4-fold) of severe toxicity from irinotecan treatment, including dose limiting diarrhea and neutropenia. However, UGT1A1 polymorphism is not the sole predictor of irinotecan clearance because of irinotecan complex metabolism and elimination (involving carboxylesterase, CYP3A4, and transporters).¹¹³

A very important deficit in glucuronidation was observed in patients with Gilbert syndrome, suggesting a genetic predisposition to the metabolism of irinotecan and an increased risk of irinotecan toxicity.¹¹⁴ It was suggested that unconjugated serum bilirubin could be a predictive parameter for irinotecan toxicity. Better still is the individualization of irinotecan dose by phenotyping of UGT 1A1 by gene diagnosis.

Most drugs used in cancer chemotherapy are metabolized by CYP3A, CYP1A, CYP2B, and CYP2C isoforms. The most abundant CYP expressed in the liver, accounting for 60% of the CYP activity, and in intestinal wall is CYP3A4. Twenty-five variant alleles for CYP3A4 have been reported to date, however, despite significant inter-individual variation genotype/phenotype studies have not shown concordance in the expression levels and activity. CYP3A5 expression is polymorphic, with readily detectable expression levels in about 30% of livers and low to undetectable levels in the rest.

CYP3A4 is involved in the metabolism of a majority of anticancer drugs, CYP3A5 polymorphisms could affect the pharmacodynamics of agents that are metabolized by both enzymes. CYP3A4 and CYP3A5 catalyze the initial oxidation (before cyclization) of docetaxel, a semisynthetic used in the treatment of breast and ovarian cancers. The contribution of the CYP3A polymorphism to the effect of anticancer drugs has not been elucidated, but because almost half of all anti-cancer drugs are CYP3A substrates, polymorphisms in CYPs are likely to affect the pharmacodynamics of anticancer drugs.¹⁰⁶

FUTURE DEVELOPMENTS

The value of clinical pharmacokinetics must be judged with regard to patient outcomes such as choosing to include the dose-limiting toxicity, taking into account the most important covariates, and selecting the best concentration-effect relationship.

Explorations may be complicated by the fact that the dose-limiting toxicity chosen, is a delayed reaction to the treatment and that toxicity, with efficacy, most often represent cumulated doses and appear only after multiple doses. Identification of at-risk subpopulations such as patients with hepatic or renal impairment would have to be taken into account when defining pharmacokinetic-pharmacodynamic relationships.¹¹⁵

In most cases so far, only the plasma concentration of parent drugs has been taken into account in the evaluation of drug-exposure. However, metabolites can present a dose-limiting toxicity too, and the nature of this toxicity can be slightly different from that of the parent drug. Similarly, drug metabolites can be therapeutically active, and therefore their blood concentration is linked to treatment efficacy (eg irinotecan and its active metabolite or methotrexate and its polyglutamated intracellular metabolites).¹¹⁶ Moreover, the analytical methods used for the TDM of anticancer drugs are largely concerned with total forms, except for platinum compounds, whereas pharmacokinetic parameters derived from plasma concentrations of the unbound forms may be better predictors of severe toxicity and therapeutic response than those derived from total forms.

New analytical methods, such as liquid chromatography combined with mass spectrometry or tandem mass spectrometry, have introduced a key improvement in specificity and sensitivity. They have been used recently for the determination of an increasing number of drugs and active metabolites in plasma or in surrogate tissues.¹¹⁷

They could be employed to routinely assess metabolites at low concentration or unbound active molecules. The development of non-invasive methods for the determination of drugs and active metabolite concentration and/or effects on tumor tissue would help to find more accurate pharmacokinetic-pharmacodynamic relationships and overcome the long lag time between the determination of drug in plasma and assessment of the ultimate pharmacodynamic effects, such as survival time or tumor size change.¹¹⁸ Nuclear magnetic resonance has been used to determine the kinetics of active molecule uptake and retention in solid tumors for fluorouracil.¹¹⁹ Another promising technique that allows determination of effects within tumors is positron emission tomography associated with a scanner.

To date, examples of TDM of anticancer drugs often stem from relationships between serum concentrations (or other exposure variables such as AUC) and toxicity, whereas the relationships with therapeutic effects are not well proven for many cancers and drugs. In the future, a better knowledge of the relationships between pharmacokinetic parameter values or exposure variables and tumor growth or survival rate, for example, will contribute to the improvement of treatment efficacy and patient's outcome by allowing an *a priori* determination of the first dose and a *posteriori* adjustment of the following doses.

There is an increasing focus on the implementation of pharmacokinetic- pharmacodynamic studies and modeling from the beginning of a drug's evaluation.¹²⁰ New chemotherapeutic agents may fail new drug development because of unfavorable pharmacokinetics as well as pharmacodynamics profiles.¹²¹ However, to date, a large number of studies provide kinetic and dynamic data without investigating the relationships between them.¹²² The critical effect of pharmacokinetic monitoring in cancer chemotherapy will depend on the ability to develop pharmacokinetic-pharmacodynamic models that take into account covariates such as disease state, concomitant treatments, pharmacokinetic behavior (eg enzyme induction or inhibition, binding to plasma proteins)¹²³ and other patient-related factors. The data set should be obtained in an ample number of patients, ensuring inclusion of the widest range of the different physiological factors influencing pharmacokinetics and pharmacodynamics, and representation of the target patient population with respect to age, gender, pathophysiological characteristics, and concurrent and previous treatments. Ideally, studies should be long enough to evaluate survival rates. Otherwise, the search for relevant and useful covariates may not be successful.¹²⁴

Specific and easier to use software, as well as a better knowledge of pharmacokinetic- pharmacodynamic methodology among clinical pharmacist, is required.¹²² Finally, circadian time of infusion should be taken into account for drugs for which recent studies have found that data such as CL, C_{max}, AUC, or protein binding were chronomodulated on a circadian basis. For example for 5-FU a chronomodulated delivery schedule using a perfusion rate inversely proportional to the circadian variations of clearance resulted in an increased effectiveness of the treatment and decreased occurrence of drug-associated side-effects.¹²⁵

Chronotherapy has been shown to be significantly less toxic and more effective than flat infusion. The concept of circadian selectivity of cancer chemotherapy is well founded and easy to implement as programmable pumps for the delivery of chemotherapy are available and they are of manageable size, weight, and cost.¹²⁶

Pharmacokinetic-pharmacodynamic modeling generally attempts to study models for a single drug, and multi-drug regimens have had little attention, although the coupled treatments can be retained as covariates in the final population model. The coupled drugs usually have different mechanisms of action

and toxicity profile, although in some cases a drug is administered to enhance the effects of another. In such cases, an alternative approach to TDM that combines pharmacokinetic and pharmacodynamic monitoring has been proposed.¹²⁷ ALL treatment protocols based on combination chemotherapy were used as a model. Different pharmacodynamic endpoints, such as the initial reduction of leukemia cells in peripheral blood or in bone marrow and the detection of minimal residual disease by immunological or polymerase chain reaction-based methods were observed to identify those who exhibited poor response to therapy. Systemic exposure was measured to determine whether poor response could result from too low an exposure to individual drugs. If systemic exposure appeared optimal, then alternative drug therapy or different treatment strategies might be tried. Ideally, a true global strategy would have required studies on pharmacodynamic interactions (eg synergy, additively, antagonism) on therapeutic as well as toxic effects, and translated them as interaction terms in the model.

MULTIDISCIPLINARY APPROACH OF TDM IN ANTICANCER DRUGS

Establishing a relationship between drug concentration and drug effect is an essential foundation for use of TDM with the ultimate goal of optimizing cancer chemotherapy.

As progress continues in this field, the justification for TDM will become gradually more convincing for selected antineoplastic agents. However, implementation of TDM requires more than just a defined therapeutic range for specific agents, it will also require a well-coordinated multidisciplinary effort. The appropriate application requires the correct administration of drug, correct collection and processing of blood samples, precise and accurate measurement of drug or active metabolites, and appropriate interpretation of results.³ The whole process involves the skill and knowledge of different professionals, including pharmacists, nurses, phlebotomists, technicians/technologists, clinical chemists, clinical pharmacists, pharmacokinetics, and physicians. Each person involved in the process must clearly understand the limitations and difficulties of TDM and make efforts to fully optimize TDM at each step; failure at any step can compromise the whole process.

THE ROLE OF CLINICAL PHARMACIST

The primary clinician chooses the initial dosing regimen for the patient and makes subsequent changes of dosage depending on clinical response, TDM, and other clinical or biochemical parameters. Hence, enough knowledge in pharmacokinetics and pharmacodynamics must be acquired to appreciate the potential and the limitations of TDM, and the sources and consequences of errors that can occur during the TDM process. Clinicians must carefully interpret results of drug concentrations, recognizing that drug measurements are only an intermediate endpoint, with clinical response being the ultimate measure of therapeutic outcome.

Well-designed clinical studies are essential to define the pharmacokinetics of medications and accurately define a therapeutic range for TDM. One of the essential roles of the science of pharmacokinetics is to construct, evaluate, and select a mathematically correct and a physiologically appropriate model for determination of pharmacokinetic parameters. The critical analysis of these parameters is essential because this determines the accuracy of the calculated pharmacokinetic parameters^{128,129} and subsequent dosage adjustments to achieve the target drug concentration. It is critical to select the appropriate pharmacodynamic models for establishing strong concentration–effect relationships, which can eventually provide the foundation for establishing ‘therapeutic ranges’ for TDM.

REFERENCES

- Rodman JH, Evans WE. Targeted systemic exposure for pediatric cancer therapy. In: D'Argenio D. ed. *Advanced Methods of Pharmacokinetic and Pharmacodynamic Systems Analysis*. 1991; New York, Plenum Press, 1991: 177–83.
- Spector R, Park GD, Johnson GF, Vesell ES. Therapeutic drug monitoring. *Clin Pharmacol Ther* 1988; 43: 345–53.
- Reynolds DJM, Aronson JK. Making the most of plasma drug concentration measurements. *Br Med J* 1993; 306: 48–51.
- Evans WE, Relling MV. Clinical pharmacokinetics–pharmacodynamics of anticancer drugs. *Clin Pharmacokinet* 1989; 16: 327–36.
- Masson E, Zamboni WC. Pharmacokinetic optimization of cancer chemotherapy. Effect on outcomes. *Clin Pharmacokinet* 1997; 32: 324–43.
- Galpin AJ, Evans WE. Therapeutic drug monitoring in cancer management. *Clin Chem* 1993; 39: 2419–30.
- DeVita VT. Principles of cancer management: chemotherapy. In: DeVita VT, Hellman S, Rosenberg SA. eds. *Cancer: Principles and Practice of Oncology* 1997; **fifth edn**, Philadelphia, Lippincott, 1997: 333–47.
- Moore MJ, Erlichman C. Therapeutic drug monitoring in oncology. Problems and potential in antineoplastic therapy. *Clin Pharmacokinet* 1987; 13: 205–27.
- Jodrell DI, Egorin MJ, Canetta RM *et al.* Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. *J Clin Oncol* 1992; 10: 520–28.
- Milano G, Roman P, Khater P, Frenay M, Renee N, Namer M. Dose versus pharmacokinetics for predicting tolerance to 5 day continuous infusion of 5-FU. *Int J Cancer* 1988; 41: 537–41.
- Milano G, Etienne MC, Renee N *et al.* Relationship between fluorouracil systemic exposure and tumor response and patient survival. *J Clin Oncol* 1994; 15: 1291–95.
- Santini J, Milano G, Thyss A *et al.* 5-FU therapeutic monitoring with dose adjustment leads to an improved therapeutic index in head and neck cancer. *Br J Cancer* 1989; 59: 287–90.
- Joel S, O'Byrne Penson K, Papamichael R *et al.* A randomized concentration-controlled comparison of standard (5-day) vs. 260A. Rousseau and P. Marquet prolonged (15-day) infusions of etoposide phosphate in small cell lung cancer. *Ann Oncol* 1998; 11: 1205–11.
- Chatelut E, Pivot X, Otto J *et al.* A limited sampling strategy for determining carboplatin AUC and monitoring drug dosage. *Eur J Cancer* 2000; 36: 264–69.
- Pignon T, Lacarelle B, Duffaud F *et al.* Pharmacokinetics of high-dose methotrexate in adult osteogenic sarcoma. *Cancer Chemother Pharmacol* 1994; 33: 420–24.
- Gamelin E, Boisdron-Celle M. Dose monitoring of 5-fluorouracil in patients with colorectal or head and neck cancer – status of the art. *Crit Rev Oncol Hematol* 1999; 30: 71–79.
- Joel SP, Ellis P, O'Byrne K *et al.* Therapeutic monitoring of continuous infusion etoposide in small-cell lung cancer. *J Clin Oncol* 1996; 14: 1903–12.
- Lennard L. Therapeutic drug monitoring of cytotoxic drugs. *Br J Clin Pharmacol* 2001; 52: 75–87.
- Rousseau A, Marquet P, Debord J, Sabot C, Lachâtre G. Adaptive control methods for dose individualization of anticancer agents. *Clin Pharmacokinet* 2000; 38: 315–53.
- Hryniuk W, Bush H. The importance of dose intensity in chemotherapy of metastatic breast cancer. *J Clin Oncol* 1984; 2: 1281–88.

- 21 Ratain MJ. Therapeutic relevance of pharmacokinetics and pharmacodynamics. *Semin Oncol* 1992; 19: 8-13.
- 22 Ratain MJ. Pharmacology of cancer chemotherapy. In: DeVita VT, Hellman S, Rosenberg SA. eds. *Cancer: Principles and Practice of Oncology* 1997; **fifth edn**, Philadelphia, Lippincott, 1997: 375-85.
- 23 Hryniuk WM, Figueredo A, Goodyear M. Applications of dose intensity to problems in chemotherapy of breast and colorectal cancer. *Semin Oncol* 1987; 14: 3-11.
- 24 Frei E, Canellos GP. Dose. A critical factor in cancer chemotherapy. *Am J Med* 1980; 69: 585-94.
- 25 Evans WE. Clinical pharmacodynamics of anticancer drugs: a basis for extending the concept of dose-intensity. *Blut* 1988; 56: 241-48.
- 26 Delepine N, Delepine G, Jasmin C, Desbois JC, Cornille H, Mathe G. Importance of age and methotrexate dosage: prognosis in children and young adults with high-grade osteosarcomas. *Biomed Pharmacother* 1988; 42: 257-62.
- 27 Bacci G, Ferrari S, Delepine N *et al*. Predictive factors of histologic response to primary chemotherapy in osteosarcoma of the extremity: study of 272 patients preoperatively treated with high-dose methotrexate, doxorubicin, and cisplatin. *J Clin Oncol* 1998; 16: 658-63.
- 28 Collins JM, Zaharko DS, Dedrick RL, Chabner BA. Potential roles for preclinical pharmacology in phase I clinical trials. *Cancer Treat Rep* 1986; 70: 73-80.
- 29 EORTC. Pharmacokinetics and metabolism group. Pharmacokinetically guided dose escalation in phase I clinical trials. Commentary and proposed guidelines. *Eur J Cancer Clin Oncol* 1987; 23: 1083-87.
- 30 Evans WE, Rodman JH, Relling MV, Crom WR, Rivera GK, Pratt CB, Crist WM. Concept of maximum tolerated systemic exposure and its application to phase I-II studies of anticancer drugs. *Med Pediatr Oncol* 1991; 19: 153-59.
- 31 Evans WE. Alternative approaches for phase I studies of anticancer drugs: a role for therapeutic drug monitoring. *Ther Drug Monit* 1993; 15: 492-97.
- 32 Workman P, Graham MA. Pharmacokinetics and cancer chemotherapy. *Eur J Cancer* 1994; 30A: 706-10.
- 33 Evans WE, Petros WP, Relling MV, Crom WR, Madden T, Rodman JH, Sunderland M. Clinical pharmacology of cancer chemotherapy in children. *Pediatr Clin North Am* 1989; 36: 1199-230.
- 34 Knoester PD, Underberg WJM, Beijnen JH. Clinical pharmacokinetics and pharmacodynamics of anticancer agents in pediatric patients [Review]. *Anticancer Res* 1993; 13: 1795-808.
- 35 Plunkett W, Gandhi V. Cellular pharmacodynamics of anticancer drugs. *Semin Oncol* 1993; 20: 50-63.
- 36 Rodman JH, Relling MV, Stewart CF, Synold TW, McLeod H, Kearns C *et al*. Clinical pharmacokinetics and pharmacodynamics of anticancer drugs in children. *Semin Oncol* 1993; 20: 18-29.
- 37 Ratain MJ, Schilsky RL, Conley BA, Egorin MJ. Pharmacodynamics in cancer therapy. *J Clin Oncol* 1990; 8: 1739-53.
- 38 Graf N, Winkler K, Betlemovic M, Fuchs N, Bode U. Methotrexate pharmacokinetics and prognosis in osteosarcoma. *J Clin Oncol* 1994; 12: 1443-51.
- 39 Graves DA, Locke CS Jr, Muir KT, Miller RP. The influence of assay variability on pharmacokinetic parameter estimation. *J Pharmacokinetic Biopharm* 1989; 17: 571-92.
- 40 Egorin MJ, Van Echo DA, Olman EA, Whitacre MY, Forrest A, Aisner J. Prospective validation of a pharmacologically based dosing scheme for the cis-diamminedichloroplatinum (II) analogue diamminecyclobutanedicarboxylatoplatinum. *Cancer Res* 1985; 45: 6502-06.
- 41 Calvert AH, Newell DR, Gumbrell LA *et al*. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989; 7: 1748-56.
- 42 Newell DR, Pearson ADJ, Balmanno K *et al*. Carboplatin pharmacokinetics in children: the development of a paediatric dosing formula. *J Clin Oncol* 1993; 11: 2314-23.
- 43 Chatelut E, Canal P, Brunner V *et al*. Prediction of carboplatin clearance from standard morphological and biological patient characteristics. *J Natl Cancer Inst* 1995; 87: 573-80.
- 44 Benezet S, Guimbaud R, Chatelut E, Chevreau C, Bugat R, Canal P. How to predict carboplatin clearance from standard morphological and biological characteristics in obese patients. *Ann Oncol* 1997; 6: 607-09.
- 45 Graf N, Winkler K, Betlemovic M, Fuchs N, Bode U. Methotrexate pharmacokinetics and prognosis in osteosarcoma. *J Clin Oncol* 1994; 12: 1443-51.
- 46 Pignon T, Lacarelle B, Duffaud F *et al*. Pharmacokinetics of high-dose methotrexate in adult osteogenic sarcoma. *Cancer Chemother Pharmacol* 1994; 33: 420-24.
- 47 Odoul F, Le Guellec C, Lamagnere JP *et al*. Prediction of methotrexate elimination after high dose infusion in children with acute lymphoblastic leukaemia using a population pharmacokinetic approach. *Fundam Clin Pharmacol* 1999; 13: 595-604.
- 48 Fety R, Rolland F, Barberi-Heyob M *et al*. Clinical impact of pharmacokinetically-guided dose adaptation of 5-fluorouracil: results from a multicentric randomized trial in patients with locally advanced head and neck carcinomas. *Clin Cancer Res* 1998; 4: 2039-45.
- 49 Gallo JM, Laub PB, Rowinski EK, Grochow LB, Baker SD. Population pharmacokinetic model for topotecan derived from phase I clinical trials. *J Clin Oncol* 2000; 18: 2459-67.

- 50 Monarzeri A, Boucaud M, Lokiec F *et al.* Population pharmacokinetics of topotecan: intra-individual variability in total drug. *Cancer Chemother Pharmacol* 2000; 46: 375-81.
- 51 Huitema AD, Mathot RA, Tibben MM, Schellens JH, Rodenhuis S, Beijnen JH. Validation of techniques for the prediction of carboplatin exposure: application of Bayesian methods. *Clin Pharmacol Ther* 2000; 67: 621-30.
- 52 Minami H, Beijnen JH, Verweij J, Ratain MJ. Limited sampling model for area under the concentration time curve of total topotecan. *Clin Cancer Res* 1996; 2: 43-46.
- 53 Stromgren AS, Sorensen BT, Jakobsen P, Jakobsen A. A limited sampling method for estimation of the etoposide area under the curve. *Cancer Chemother Pharmacol* 1993; 32: 226-30.
- 54 Ratain MJ, Robert J, Van Der Vijgh WJ. Limited sampling models for doxorubicin pharmacokinetics. *J Clin Oncol* 1991; 9: 871-76.
- 55 Sorensen BT, Stromgren A, Jakobsen P, Jakobsen A. A limited sampling method for estimation of the carboplatin area under the curve. *Cancer Chemother Pharmacol* 1993; 31: 324-27.
- 56 Miyazaki M, Fujiwara Y, Takahashi T *et al.* Limited-sampling models for estimation of the carboplatin area under the curve. *Anticancer Res* 1997; 17: 4571-75.
- 57 Egorin MJ, Forrest A, Belani CP, Ratain MJ, Abrams JS, Van Echo DA. A limited sampling strategy for cyclophosphamide pharmacokinetics. *Cancer Res* 1989; 49: 3129-33.
- 58 Mick R, Gupta E, Vokes VV, Ratain MJ. Limited-sampling models for irinotecan pharmacokinetics-pharmacodynamics: prediction of biliary index and intestinal toxicity. *J Clin Oncol* 1996; 14: 2012-19.
- 59 Beal SL, Sheiner LB (Eds.) NONMEM. Users Guides. University of California, San Francisco, CA, 1994.
- 60 Karlsson MO, Jonsson EN, Wiltse CG, Wade JR. Assumption testing in population pharmacokinetic models: illustrated with an analysis of moxonidine data from congestive heart failure patients. *J Pharmacokinet Biopharm* 1998; 26: 207-45.
- 61 Mallet A. A maximum likelihood estimation method for random coefficient regression. *Biometrika* 1986; 73: 645-56.
- 62 Schumitsky A. Nonparametric EM algorithms for estimating prior distributions. *App Math Comput* 1991; 45: 141-57.
- 63 Jelliffe RW, Schumitzky A, Van Guilder M, Jiang F. Manual for the USC*Pack Collection of PC Programs. Laboratory of Applied Pharmacokinetics, School of Medicine 1995; Los Angeles, CA, University of Southern California, 1995.
- 64 Jelliffe RW, Schumitzky A, Bayard D *et al.* Model-based, goal oriented individualized drug therapy. *Clin Pharmacokinet* 1998; 34: 57-77.
- 65 Iliadis A, Bachir-Raho M, Bruno R, Favre R. Bayesian estimation and prediction of clearance in high-dose methotrexate infusions. *J Pharmacokinet Biopharm* 1985; 13: 101-15.
- 66 Sabot C, Debord J, Rouillet B *et al.* Bayesian estimation and population pharmacokinetic parameters of high dose methotrexate in osteosarcoma. *Clin Res Reg Affairs* 1993; 10: 233-41.
- 67 Sabot C, Debord J, Rouillet B, Marquet P, Merle L, Lachatre G. Comparison of 2- and 3-compartment models for Bayesian estimation of methotrexate pharmacokinetics. *Int J Clin Pharmacol Ther* 1995; 33: 164-69.
- 68 Pignon T, Lacarelle B, Duffaud F *et al.* Dosage adjustment of high dose methotrexate using Bayesian estimation: a comparative study of two different concentrations at the end of 8-h infusions. *Ther Drug Monit* 1995; 17: 164-69.
- 69 Peng B, Boddy AV, Cole M *et al.* Comparison of methods for the estimation of carboplatin pharmacokinetics in paediatric cancer patients. *Eur J Cancer* 1995; 31: 1804-10.
- 70 Johansen MJ, Madden T, Mehra RC *et al.* Phase I pharmacokinetic study of multicycle high-dose carboplatin followed by peripheral-blood stem-cell infusion in patients with cancer. *J Clin Oncol* 1997; 15: 1481-91.
- 71 Doz F, Urien S, Chatelut E *et al.* A limited-sampling method for evaluation of the area under the curve of ultrafilterable carboplatin in children. *Cancer Chemother Pharmacol* 1998; 42: 250-54.
- 72 Guillet P, Monjanel S, Nicoara A *et al.* A Bayesian dosing method for carboplatin given by continuous infusion for 120 h. *Cancer Chemother Pharmacol* 1997; 40: 143-49.
- 73 Favre R, Charbit M, Rinaldi Y, Iliadis A, Cano JP, Carcassonne Y. La pharmacocinétique dans les études de phase IV pour la prévision du schéma thérapeutique. *Bull Cancer* 1988; 75: 541-50.
- 74 Evène E, Chatelut E, Tranchand B *et al.* Estimation bayésienne des paramètres pharmacocinétiques de l'étoposide. *Bull Cancer* 1997; 84: 699-703.
- 75 Tranchand B, Amsellem C, Chatelut E *et al.* A limited-sampling strategy for estimation of etoposide pharmacokinetics in cancer patients. *Cancer Chemother Pharmacol* 1999; 43: 316-22.
- 76 Rodman JH, Furman WL, Sunderland M, Rivera G, Evans WE. Escalating etoposide systemic exposure to increase dose intensity for paediatric cancer patients. *J Clin Oncol* 1993; 11: 287-93.
- 77 Launay MC, Milano G, Iliadis A, Frenay M, Namer N. A limited sampling procedure for estimating Adriamycin pharmacokinetics in cancer patients. *Br J Cancer* 1989; 60: 89-92.

- 78 Bressolle F, Ray P, Jacquet JM *et al.* Bayesian estimation of doxorubicin pharmacokinetic parameters. *Cancer Chemother Pharmacol* 1991; 29: 53-60.
- 79 Marchiset-Leca D, Leca FR, Galeani A, Noble A, Iliadis A. A limited sampling strategy for the study of pirarubicin pharmacokinetics in human. *Cancer Chemother Pharmacol* 1995; 36: 233-38.
- 80 Yamamoto N, Tamura T, Karato A *et al.* CPT-11: population pharmacokinetic model and estimation of pharmacokinetics using the Bayesian method in patients with lung cancer. *Jpn J Cancer Res* 1994; 85: 972-77.
- 81 Nakashima H, Lieberman R, Karato A *et al.* Efficient sampling strategies for forecasting pharmacokinetic parameters of irinotecan (CPT-11): implication for area under the concentration time curve monitoring. *Ther Drug Monit* 1995; 17: 221-29.
- 82 Furman WL, Baker SD, Pratt CB, Rivera GK, Evans WE, Stewart CF. Escalating systemic exposure of continuous infusion topotecan in children with recurrent acute leukemia. *J Clin Oncol* 1996; 14: 1504-11.
- 83 Crom WR, de Graaf SS, Synold T *et al.* Pharmacokinetics of vincristine in children and adolescents with acute lymphocytic leukemia. *J Pediatr* 1994; 125: 642-49.
- 84 Sabot C, Marquet P, Debord J, Carpentier N, Merle L, Lachâtre G. Bayesian pharmacokinetic estimation of vinoreline in non-small lung cancer patients. *Eur J Clin Pharmacol* 1998; 54: 171-75.
- 85 Gauvin A, Pinguet F, Culine S, Astre C, Gomeni R, Bressolle F. Bayesian estimate of vinorelbine pharmacokinetic parameters in elderly patients with advanced metastatic cancer. *Clin Cancer Res* 2000; 6: 2690-95.
- 86 Jodrell DI, Reyno LM, Sridhara R *et al.* Suramin: development of a population pharmacokinetic model and its use with intermittent short infusions to control plasma drug concentration in patients with prostate cancer. *J Clin Oncol* 1994; 12: 166-75.
- 87 Eisenberger MA, Sinibaldi VJ, Reyno LM *et al.* Phase I and clinical evaluation of a pharmacologically guided regimen of suramin in patients with hormone-refractory prostate cancer. *J Clin Oncol* 1995; 13: 2174-86.
- 88 Nguyen L, Tranchand B, Puozzo C, Variol P. Population pharmacokinetics model and limited sampling strategy for intravenous vinorelbine derived from phase I clinical trials. *Br J Clin Pharmacol* 2002; 53: 459-68.
- 89 Variol P, Nguyen L, Tranchand B, Puozzo C. A simultaneous oral/intravenous population pharmacokinetic model for vinorelbine. *Eur J Clin Pharmacol* 2002; 58: 467-76.
- 90 Urien S, Lokiec F. Population pharmacokinetics of total and unbound plasma cisplatin in adult patients. *Br J Clin Pharmacol* 2004; 57: 756-63.
- 91 de Jongh FE, Gallo JM, Shen M, Verweij J, Sparreboom A. Population pharmacokinetics of cisplatin in adult cancer patients. *Cancer Chemother Pharmacol* 2004; 54: 105-12.
- 92 Slaviero KA, Clarke SJ, McLachlan AJ, Blair EYL, Rivory LP. Population pharmacokinetics of weekly docetaxel in patients with advanced cancer. *Br J Clin Pharmacol* 2003; 57: 44-53.
- 93 Launay-Iliadis MC, Bruno R, Cosson V, Vergniol JC *et al.* Population pharmacokinetics of docetaxel during phase I studies using nonlinear mixed-effect modeling and nonparametric maximum-likelihood estimation. *Cancer Chemother Pharmacol* 1995; 37: 47-54.
- 94 Falcone A, Pfanner E, Cianci C *et al.* Suramin in patients with metastatic colorectal cancer pretreated with fluoropyrimidine based chemotherapy. *Cancer* 1995; 75: 440-43.
- 95 Odoul F, Le Guellec C, Lamagnère JP *et al.* Prediction of methotrexate elimination after high dose infusion in children with acute lymphoblastic leukemia using a population pharmacokinetic approach. *Fundam Clin Pharmacol* 1999; 13: 595-604.
- 96 Ensom MH, Davis GA, Cropp CD *et al.* Clinical pharmacokinetics in the 21st century. *Clin Pharmacokinet* 1998; 34: 265-79.
- 97 Evans WE, Relling MV, Rodman JH *et al.* Conventional compared with individualized chemotherapy for childhood acute lymphoblastic leukemia. *N Engl J Med* 1998; 338: 499-505.
- 98 Fety R, Rolland F, Barberi-Heyob M *et al.* Clinical impact of pharmacokinetically-guided dose adaptation of 5-fluorouracil: results from a multicentric randomized trial in patients with locally advanced head and neck carcinomas. *Clin Cancer Res* 1998; 4: 2039-45.
- 99 Evans WE, McLeod HL. Pharmacogenomics - drug disposition, drug targets, and side effects. *N Engl J Med* 2003; 348: 538-49.
- 100 Nagasubramanian R, Innocenti F, Ratain MJ. Pharmacogenetics in cancer treatment. *Annu Rev Med* 2003; 54: 437-52.
- 101 Marsh S, McLeod HL. Cancer pharmacogenetics. *Br J Cancer* 2004; 90: 8-11.
- 102 Houyau P, Gay C, Chatelut E *et al.* Severe fluorouracil toxicity in a patient with dihydropyrimidine dehydrogenase deficiency [letter]. *J Natl Cancer Inst* 1993; 85: 1602-03.
- 103 Meinsma R, Fernandez-Salguero P, van Kulenberg AB *et al.* Human polymorphism in drug metabolism: mutation in the dihydropyrimidine dehydrogenase gene results in exon skipping and thymine uraciluria. *DNA Cell Biol* 1995; 14: 1-6.
- 104 Takai S, Fernandez-Salguero P, Kimura S *et al.* Assignment of the human dihydropyrimidine dehydrogenase gene to chromosome region 1p22 by fluorescence in situ hybridisation. *Genomics* 1994; 24: 613-14.
- 105 Albin N, Jonhson MR, Shahinian H *et al.* Initial characterization of the molecular defect in human

- dihydropyrimidine dehydrogenase deficiency. *Proc Am Assoc Cancer Res* 1995; 36: 211.
- 106 Topic Elizabeta Pharmacogenetic and Tumour Drugs - 2005 <http://www.ifcc.org/ejifcc/vol16no2/160206200512.htm>
 - 107 Lennard L. The clinical pharmacology of 6-mercaptopurine. *Eur J Clin Pharmacol* 1992; 43: 329-39.
 - 108 Lennard L, Lilleyman JS, Van Loon J *et al.* Genetic variation in response to 6-mercaptopurine for childhood acute lymphoblastic leukaemia. *Lancet* 1990; 336: 225-29.
 - 109 Klemetsdal B, Tollefsen E, Loennechen T *et al.* Interethnic difference in thiopurine methyltransferase activity. *Clin Pharmacol Ther* 1992; 51: 24-31.
 - 110 Krynetski EY, Tai HL, Yates CR, Fessing MY, Loennechen T, Schuetz JD *et al.* Genetic polymorphism of thiopurine S-methyltransferase: clinical importance and molecular mechanisms. *Pharmacogenetics* 1996; 6: 279-90.
 - 111 Chabot GG. Clinical pharmacokinetics of irinotecan. *Clin Pharmacokinet* 1997; 33: 245-59.
 - 112 Iyer L, King CD, Whittington PR *et al.* Genetic predisposition to the metabolism of irinotecan (CPT-11): Role of uridine diphosphate glucuronosyltransferase isoform 1A1 in the glucuronidation of its active metabolite (SN-38) in human liver microsomes. *J Clin Invest* 1998; 101: 847-54.
 - 113 Ando Y, Saka H, Asai G *et al.* UGT1A1 genotypes and glucuronidation of SN-38, the active metabolite of irinotecan. *Ann Oncol* 1998; 9: 845-47.
 - 114 Wasserman E, Myara A, Lokiec F *et al.* Severe CPT-11 toxicity in patients with Gilbert's syndrome: two case reports. *J Clin Invest* 1997; 8: 1049-51.
 - 115 Canal P, Chatelut E, Guichard S. Practical treatment guide for dose individualisation in cancer chemotherapy. *Drugs* 1998; 56: 1019-38.
 - 116 Chabner BA, Allegra CJ, Curt GA *et al.* Polyglutamation of methotrexate: is methotrexate a prodrug? *J Clin Invest* 1985; 76: 907-12.
 - 117 Marquet P, Lachatre G. Liquid chromatography-mass spectrometry: potential in forensic and clinical toxicology. *J Chromatogr B* 1999; 733: 93-118.
 - 118 Hon YY, Evans WE. Making TDM work to optimize cancer chemotherapy: a multidisciplinary team approach. *Clin Chem* 1998; 44: 388-400.
 - 119 Maxwell R. New techniques in the pharmacokinetic analysis of cancer drugs: III. Nuclear magnetic resonance. *Cancer Surv* 1993; 17: 415-23.
 - 120 Ranson MR, Scarffe JH. Population and Bayesian pharmacokinetics in oncology. *Clin Oncol* 1994; 6: 254-60.
 - 121 Masson A, Zamboni WC. Pharmacokinetic optimization of cancer chemotherapy: effects on outcomes. *Clin Pharmacokinet* 1997; 32: 324-43.
 - 122 Bellissant E, Sébille V, Painsaud G. Methodological issues in pharmacokinetic-pharmacodynamic modeling. *Clin Pharmacokinet* 1998; 35: 151-66.
 - 123 Vozeh S, Steimer JL, Rowland M *et al.* The use of population pharmacokinetics in drug development. *Clin Pharmacokinet* 1996; 30: 81-93.
 - 124 Levy G. Predicting effective drug concentrations for individual patients: determinants of pharmacodynamic variability. *Clin Pharmacokinet* 1998; 34: 323-33.
 - 125 Bruguerolle B. Chronopharmacokinetics: current status. *Clin Pharmacokinet* 1998; 35: 83-94.
 - 126 Bressolle F, Joulia JM, Pinguet F, Ychou M *et al.* Circadian rhythm of 5-fluorouracil population pharmacokinetics in patients with metastatic colorectal cancer. *Cancer Chemother Pharmacol* 1999; 44: 295-302.
 - 127 Yates CR, Pui CH, Evans WE. Pharmacodynamic monitoring of cancer chemotherapy: childhood acute lymphoblastic as a model. *Ther Drug Monit* 1998; 20: 453-8.
 - 128 Karlsson MO, Molnar V, Bergh J *et al.* A general model for time-dissociated pharmacokinetic-pharmacodynamic relationships exemplified by paclitaxel myelosuppression. *Clin Pharmacol Ther* 1998; 63: 11-25.
 - 129 Minami H, Sasaki Y, Saijo N *et al.* Indirect-response model for the time course of leukopenia with anticancer drugs. *Clin Pharmacol Ther* 1998; 64: 511-21.

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Appendix AMIRI02

EDITORIALS

Why Do Phase III Clinical Trials in Oncology Fail so Often?

Laleh Amiri-Kordestani, Tito Fojo

Correspondence to: Tito Fojo, MD, PhD, Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bldg 10, Rm 12N226, 9000 Rockville Pike, Bethesda, MD 20892 (e-mail: fojot@mail.nih.gov).

Achieving success in the development of a cancer drug continues to be challenging. Given the increasing costs (1) and the small number of drugs that gain regulatory approval (2), it is crucial to understand these failures. In this issue of the Journal, Gan et al. (3) reviewed 235 recently published phase III randomized clinical trials (RCTs). They report that 62% of the trials did not achieve results with statistical significance. Trying to explain the high failure rate, they note the actual magnitude of benefit achieved in a clinical trial (designated B) is nearly always less than what was predicted at the time the trial was designed (designated δ) and conclude, “investigators consistently make overly-optimistic assumptions regarding treatment benefits when designing RCTs.”

But really should we be surprised that phase III trials, the venue for detecting “small” differences, so often disappoint? Almost by definition, phase III studies are designed to detect small differences (4,5). The problem is that small has given way to “marginal” as outcomes have fallen below our already modest expectations. And who or what is to blame? Are investigators really overly optimistic regarding experimental therapies and, as the authors suggest, responsible for the large number of negative studies? Although we agree that optimism regarding clinical benefit may lead to an underpowered trial, we disagree that optimistic investigators are those we should blame. We would ask, how do Gan et al. (3) define optimism? Where do they place the line between an optimistic and a realistic expectation? The authors demonstrated a poor correlation between the expected and observed benefits but in the majority of trials also found the “expected benefits” were less than 4 months—a duration many would argue represents a modest and defensible expected benefit for the majority of solid tumors. So that, rather than excessive optimism, we believe several factors including inaccurate assessments of “limited data from early phase trials and/or investigators’ experience” interpreted in what the authors themselves acknowledge “is usually an empirical process” lead to the differences that Gan et al. (3) found between the actual (B) and predicted (δ) benefit. Although there are models that use the results of phase I/II trials to predict the outcome of phase III studies, no model is perfect (6–8). For example, the response rate, which is part of the limited dataset available in designing phase III trials, has been correlated with survival and clinical benefit (9,10). But other factors such as the duration of response make response rate less reliable and lead to discrepancy in the results of phase II and III studies (11). Similarly, the rate of stable disease and the “clinical benefit rate,” two measures increasingly reported in early phase studies, have never been shown to correlate with outcomes yet are regarded by many as measures of efficacy (12–14). Hence, we would argue that inaccurate assessments of limited data and

reliance on endpoints that have not been validated are likely more important than overoptimism.

To be sure, Gan et al. (3) recognize it is not just about statistical validity when they acknowledge “significant benefit could also result from overpowered studies that detect differences that are not clinically meaningful.” Noting that their data showed many positive studies in which the observed difference was less than predicted but still statistically significant, they wonder, as have others, whether these “positive” studies merit regulatory approval in the absence of additional supporting data (15).

We agree with the authors’ opinion that more research is needed to determine how to better define δ ; a goal they suggest might be achieved by “using statistical modeling rather through empiricism.” But pending the outcome of that research, they advocate more frequent use of interim analyses with options of early study termination for futility or efficacy and adaptive trial designs. In regards to the latter, they note, “up to 50% of RCTs that do not show a statistically significant benefit might actually be false-negative trials.” Their suggestion that these studies did not enroll enough patients and are underpowered because of unreliable δ values has the inherent assumption that marginal benefits matter. But with 100 275 patients enrolled in 158 negative trials, and an average trial size of 635 patients, many would not consider the magnitude of benefit missed to be “clinically meaningful” or worth the enrollment of hundreds of additional patients to confirm. Furthermore, their assertion that “if δ is set unrealistically high, the trial will be underpowered to detect a smaller but still clinically meaningful benefit, resulting in a negative trial” assumes that marginal differences can confer clinically meaningful benefit, an assumption with which we disagree (14,16).

It is interesting how so much is reported and can be analyzed about what constitutes a “statistically significant benefit”; yet, so little is reported or devoted to assess the statistical validity of toxicity and the risk to benefit ratio of a therapy. Indeed, one would be hard-pressed to find an experimental arm deemed statistically superior in terms of efficacy described as anything but tolerable. Unfortunately, increasingly it appears that any toxicity is tolerable or acceptable provided some gain, no matter how marginal, is achieved. But as efficacy gains become increasingly smaller, toxicity becomes increasingly important. And as Gan et al. (3) remind us, unfortunately for cancer patients, toxicity is all too often more than a grade 1 rash. Toxicity can be both severe and life altering and unfortunately at times is accompanied by a statistically inferior outcome. Remarkably, among 158 negative studies, Gan et al. found a trend toward detriment in the experimental arm in 42

studies and a statistically significant detriment in eight RCTs that enrolled 5287 patients.

The observation that trials with industry funding were more likely to be positive and associated with a small but statistically significant increased risk of detriment in the experimental arm is of concern. Their greater likelihood to achieve a positive outcome may well reflect their larger trial size because of better funding. We can only speculate as to why there would be an increased risk of detriment in the experimental arm, but the possibility that toxicity emerging in phase I/II trials would be less likely to derail a product in which a substantive investment has been made cannot be discounted. Furthermore, targeted agents—the principal if not exclusive components of the portfolios of all major companies—were no better when toxicity in the experimental arm was concerned. Because targeted agents will dominate the oncology enterprise for the rest of this decade, these observations are discouraging.

Although our goals may initially be lofty, they eventually meet reality. And in cancer drug development, reality is all too often failure (2). The challenge in oncology is to be sure that we remain focused on true clinical benefit—prolonging life. Our goals must remain lofty, and we must remember that marginal benefit should never be that goal (14,16). We need to be vigilant and as soon as it becomes apparent that any benefit will be marginal, we must discard that strategy and move on, ensuring we do not redefine failure as success. The data of Gan et al. (3) warn us that we are at risk of losing our focus. Conducting larger trials, doing more interim analyses, or using adaptive trial designs are not the solutions (17–19). We do not need more marginal results that are then pronounced “new treatment paradigms” or a “new standard of therapy.” What we need are meaningful goals and better drugs—much better drugs aimed at targets that are really important!

References

- Collier R. Rapidly rising clinical trial costs worry researchers. *CMAJ*. 2009;180(3):277–278.
- Bates SE, Amiri-Kordestani L, Giaccone G. Drug development: portals of discovery. *Clin Cancer Res*. 2012;18(1):23–32.
- Gan HK, You B, Pond GR, Chen EX. Assumptions of expected benefits in randomized phase III trials evaluating systemic treatments for cancer. *J Natl Cancer Inst*. 2012;104(8):590–598.
- Wu W, Shi Q, Sargent DJ. Statistical considerations for the next generation of clinical trials. *Semin Oncol*. 2011;38(4):598–604.
- Hoering A, Leblanc M, Crowley JJ. Randomized phase III clinical trial designs for targeted agents. *Clin Cancer Res*. 2008;14(14):4358–4367.
- Claret L, Girard P, Hoff PM, et al. Model-based prediction of phase III overall survival in colorectal cancer on the basis of phase II tumor dynamics. *J Clin Oncol*. 2009;27(25):4103–4108.
- Chen TT, Chute JP, Feigal E, Johnson BE, Simon R. A model to select chemotherapy regimens for phase III trials for extensive-stage small-cell lung cancer. *J Natl Cancer Inst*. 2000;92(19):1601–1607.
- Bruno R, Lu JF, Sun YN, Claret L. A modeling and simulation framework to support early clinical drug development decisions in oncology. *J Clin Pharmacol*. 2011;51(1):6–8.
- Tsujino K, Shiraishi J, Tsuji T, et al. Is response rate increment obtained by molecular targeted agents related to survival benefit in the phase III trials of advanced cancer? *Ann Oncol*. 2010;21(8):1668–1674.
- Buyse M, Thirion P, Carlson RW, Burzykowski T, Molenberghs G, Piedbois P. Relation between tumour response to first-line chemotherapy and survival in advanced colorectal cancer: a meta-analysis. Meta-Analysis Group in Cancer. *Lancet*. 2000;356(9227):373–378.
- Pazdur R. Response rates, survival, and chemotherapy trials. *J Natl Cancer Inst*. 2000;92(19):1552–1553.
- Vidaurre T, Wilkerson J, Simon R, Bates SE, Fojo T. Stable disease is not preferentially observed with targeted therapies and as currently defined has limited value in drug development. *Cancer J*. 2009;15(5):366–373.
- Tolcher AW. Stable disease is a valid end point in clinical trials. *Cancer J*. 2009;15(5):374–378.
- Ohorodnyk P, Eisenhauer EA, Booth CM. Clinical benefit in oncology trials: is this a patient-centred or tumour-centred end-point? *Eur J Cancer*. 2009;45(13):2249–2252.
- Ocana A, Tannock IF. When are “positive” clinical trials in oncology truly positive? *J Natl Cancer Inst*. 2011;103(1):16–20.
- Booth CM, Ohorodnyk P, Eisenhauer EA. Call for clarity in the reporting of benefit associated with anticancer therapies. *J Clin Oncol*. 2009;27(33):e213–e214.
- Emerson SS, Fleming TR. Adaptive methods: telling “the rest of the story”. *J Biopharm Stat*. 2010;20(6):1150–1165.
- Chow SC, Corey R. Benefits, challenges and obstacles of adaptive clinical trial designs. *Orphanet J Rare Dis*. 2011;6:79.
- Berry DA. Adaptive clinical trials in oncology. *Nat Rev Clin Oncol*. 2011.

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The authors have no conflicts to disclose.

Affiliation of authors: Medical Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD.

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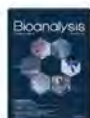
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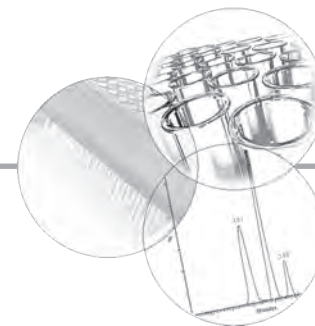
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Therapeutic drug monitoring in cancer chemotherapy

For a select number of drugs, proper management of patients includes monitoring serum or plasma concentrations of the drugs and adjusting the doses accordingly – this practice is referred to as therapeutic drug monitoring (TDM). The need for TDM arises when pharmacokinetic variability of drugs is not easily accounted for by common clinical parameters. Many chemotherapeutic drugs have large interindividual variability, yet TDM is not commonplace in chemotherapy management. This review will discuss pharmacokinetics in the context of chemotherapeutic drugs, examine the few instances where TDM is currently used in the field of oncology and propose other drugs where TDM might be useful for dose adjustments in the management of chemotherapy.

Introduction & therapeutic drug monitoring basics

The number of treatment options available in cancer chemotherapy has rapidly increased in recent years, yet this field has historically relied on an antiquated approach to individualized drug dosing based on body size measurements (mg/m^2) or weight (kg) and continues to do so in today's clinical environment. This practice has largely developed out of the toxicology concept of species scaling, where pharmacological effects can be related to body size, often log-transformed [1]. Despite dose correction based on body size, the degree of interpatient variation in clinical outcomes following standard doses of chemotherapy is large and plasma concentration of cytotoxic drugs may vary up to 14-fold or even 100-fold in the case of 5-fluorouracil (5-FU) [1]. In order to decrease interindividual pharmacokinetic differences, drug doses should ideally be tailored to the individual patient not by body surface area (BSA), but by plasma concentrations of the drug (i.e., **therapeutic drug monitoring** [TDM]). If significant relationships between blood concentrations of a particular chemotherapeutic drug and clinical efficacy of a therapeutic regimen can be established, the development of TDM strategies will lead to the selection of an optimal regimen and dose for each individual patient based on drug **pharmacokinetics**.

Therapeutic drug monitoring has been utilized for the clinical management of patients since the early 1960s [2]. Currently, TDM has widespread application in many different drug classes, such as antiepileptics, cardioactive drugs, bronchodilators, antibiotics,

antiretrovirals, antipsychotics, antimetabolites and immunosuppressants. TDM entails the measurement and interpretation of drug concentration in biological fluids for individualization of drug dosages or schedules to maximize therapeutic effects, minimize toxicities or both [2]. Theoretically, a drug should meet several criteria for TDM to be useful, some of which are listed in **Box 1**.

Compared with other drug classes, TDM has seen limited use for chemotherapeutic drugs, except for the routine monitoring of methotrexate (MTX), along with limited monitoring of busulfan and azothioprine. Based on criteria 1–3 listed in **Box 1**, many chemotherapeutic agents appear to be candidates for TDM. However, studies to investigate the utility of TDM in chemotherapy are challenging for many reasons, including the fact that assays for many of these agents are not widely available. The utility of TDM is also limited by the lack of established therapeutic concentration target ranges – there is often no established relationship between blood concentration or drug exposure and clinical efficacy. However, it should be noted that the relationship between drug exposure and toxicity is frequently well established because toxic effects are related to systemic exposure to a drug, as described by general PK parameters. Additionally, the routine use of combination therapy in oncology patients makes establishing relationships between drug concentration and therapeutic end points difficult.

This review will discuss chemotherapy pharmacokinetics by reviewing some of the current approaches to chemotherapy dosing and

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KEY TERMS

Therapeutic drug monitoring: Measuring the blood concentration of a drug and coordinating that concentration with a target concentration related to desired clinical effects

Pharmacokinetics: Study of the time–concentration relationship of drugs in the body (i.e., ‘what the body does to the drug’)

Box 1. Criteria for therapeutic drug monitoring.

- Significant inter- or intra-individual pharmacokinetics variability.
- Defined relationship between blood concentration and pharmacological effects.
- Narrow therapeutic index.
- Availability of a precise and accurate assay.

describing the sources of potential pharmacokinetic variability. In addition, this paper will investigate the current applications of TDM in cancer chemotherapy and explore potential future candidates for TDM based on current research.

Pharmacokinetics

■ Pharmacokinetics basics

The pharmacological effect of a drug is elicited by direct interaction of the drug with a receptor controlling a specific function, or by a drug-mediated alteration of the physiological process regulating the function [3]. Studies have shown that for many drugs a strong correlation exists between the serum drug concentration and the observed pharmacological effect [3]. In pharmacokinetic studies, it is assumed that changes in drug concentration in blood versus time are proportional to changes in local concentrations at the receptor site or body tissue. This assumption is called the property of kinetic homogeneity and is applicable to all pharmacokinetic models in post-absorptive and post-distributive phases of the time course [3]. The property of kinetic homogeneity is an important assumption in TDM because it is the basis on which all therapeutic and toxic concentration reference values are established.

Pharmacokinetics is the study of how the body processes and, ultimately, eliminates drugs and includes the analysis of absorption, distribution, metabolism and elimination. Below is a brief exploration of these major areas of pharmacokinetics in the context of cancer chemotherapy. A summary of the major aspects of pharmacokinetics and the potential impact of polypharmacy is shown in **FIGURE 1**.

■ Absorption

Most chemotherapeutic agents are administered intravenously or orally. The fraction of a drug that is absorbed into the systemic circulation after oral administration is referred to as the bioavailability. Intravenous administration

of a drug directly introduces it into the systemic circulation and results in rapid and complete bioavailability.

For oral administration to be useful, the bioavailability of a drug must be great enough that the active component will quickly and efficiently pass from the gastrointestinal system into the systemic circulation. Bioavailability must typically be greater than 70% for oral administration of drugs to be considered useful [3]. The absorption process depends on the drug dissociating from its dosed form (liberation), dissolving into gastrointestinal fluids and diffusing across biological membranes into the bloodstream [3]. After entering the portal circulation, the drug is also subjected to first-pass metabolism by the liver. As a result, oral agents typically have a far greater pharmacokinetic variability than intravenous agents. A particularly good example of this is demonstrated in a study of etoposide, an epipodophyllotoxin used in testicular and lung cancers. The coefficient of variation for the AUC for oral versus intravenous administration of etoposide was shown to be 58 and 28%, respectively [4]. Due to the risk of subtherapeutic drug concentrations, etoposide is uniformly administered intravenously when used for testicular cancers.

■ Drug distribution

Once a drug enters the circulation, it interacts with carrier proteins, such as albumin and α 1-acid glycoprotein (AAG), and is carried by various transport processes to different organs and tissues. The equilibrium that exists between protein-bound and free drug is one important factor in determining overall drug distribution. Only the free (unbound) drug fraction is able to cross cellular membranes and elicit a biological response. The protein-binding characteristics of a drug can have a profound influence on the distribution and elimination of that drug and on the manner in which steady state concentrations are interpreted. Acidic drugs are typically bound primarily to albumin and basic drugs are largely bound to α 1-AAG [3].

Due to the influence that drug–protein binding can have on drug distribution, differences in plasma protein levels can result in pharmacokinetic variability. As an example, malnutrition and liver metastases can cause a significant decrease in serum albumin, which can lead to an increase in unbound drug. Conversely, inflammatory conditions may increase drug–protein binding due to increased levels of α 1-AAG and other acute phase reactants [5].

■ Metabolism

The liver is the principle organ responsible for drug metabolism and plays a crucial role in pharmacokinetic variability. Once a drug is distributed into the liver by transporter proteins, the drug can be biotransformed by phase I (chemical alteration) and/or phase II (conjugation) reactions before elimination. The polymorphic genes of transporter proteins as well as phase I and phase II enzymes are a major source of interindividual pharmacokinetic variability.

Hepatic uptake

Organic anion-transporting polypeptide (OATP) proteins are a family of transporter proteins that move drugs from the circulation into hepatocytes. A study by Nozawa *et al.* has shown that OATP1B1 is involved in the hepatic disposition of SN-38 (active metabolite of irinotecan; 7-ethyl-10 hydroxycamptothecin) and that genetic polymorphisms of OATP1B1 may contribute to the known interpatient variability in the disposition of irinotecan [6]. Among the variants examined by Nozawa, the OATP1B1*15 reported allele frequency of 10–15% and exhibited decreased SN-38 transport activities.

Phase I metabolism

Phase I 'nonsynthetic' metabolism modifies the drug's chemical structure through oxidation, reduction, hydrolysis, cyclization and decyclization reactions. Of particular importance is the cytochrome P (CYP) 450 isoenzyme family, which plays a dominant role in oxidative reactions in phase I metabolism. Important isoforms for anticancer drugs include CYP1A, CYP2B, CYP2C and CYP3A [7]. According to Baker *et al.*, CYP3A activities in patients with advanced cancer demonstrated a 14-fold variation in a population of 134 patients [7]. This study's multivariate analysis concluded that C-reactive protein, as well as concomitant use of other drugs, food constituents and complementary and alternative medicines had either inhibitory or inductive effects on CYP3A in their patient population. Another example of phase I metabolism is cytochrome CYP2C19, an enzyme involved in the metabolism of the chemotherapeutic agent cyclophosphamide. Cyclophosphamide is used to treat both lymphoma and breast cancer patients. One study has demonstrated that CYP2C19 reduced activity in patients with advanced metastatic cancer [8].

Phase II metabolism

Phase II conjugation reactions are usually detoxification reactions that involve conjugation of glucuronide, acetate, glutathione, methyl, glucose, sulfate or methionine to the polar functional groups of phase I metabolites. Products of conjugation reactions have increased molecular weight and are typically inactive. One of the most well-studied chemotherapy agents metabolized by phase II metabolism is irinotecan. Pharmacokinetic variations of UDP-glucuronosyltransferases (UGTs) involve polymorphic variants in which transcriptional efficiency correlated with TA repeats in the TATA box of UGT1A1 and could lead to variations in plasma concentrations of irinotecan [9,10].

■ Drug elimination

Excretion of chemotherapeutic agent occurs mainly through the biliary tract and kidney. Elimination through pathways such as lungs, skin, sweat and tears are negligible.

Biliary excretion

A source of biliary excretion of amphipathic and lipid soluble chemotherapeutic agents is through ATP-binding cassette (ABC) transporters

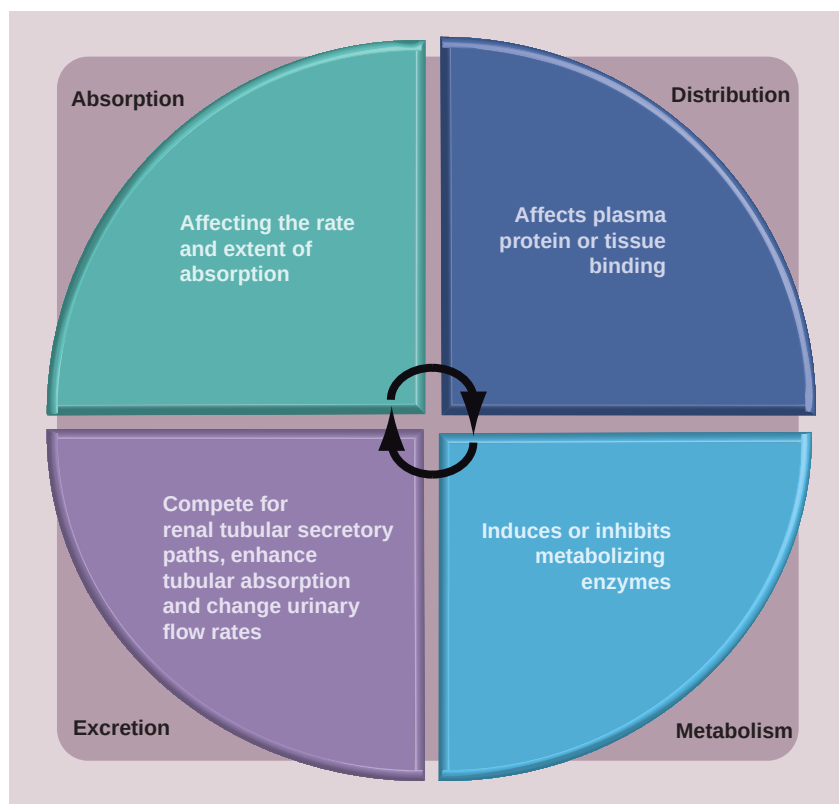


Figure 1. Potential impact of polypharmacy on pharmacokinetic parameters. Summary of aspects of absorption, distribution, metabolism and excretion.

ABCB1 and ABCC2 [6]. ABCB1 is involved in the transport of amphipathic and lipid soluble drugs, whereas ABCC2 is mainly involved in the excretion of conjugate metabolites. Specific polymorphisms of ABCB1 and ABCC2 can influence disposition and tumor response to irinotecan by regulating transported activity, as shown in patients with advanced small-cell lung cancer [11]. Other causes of pharmacokinetic variability include disease processes affecting the liver and its synthetic abilities. For example, mechanical obstruction by hepatic metastasis has been associated with decreased excretion of chemotherapeutic agents [12,13].

Renal clearance

Renal clearance is another major route for drug elimination. Two examples of pharmacokinetic variability in drugs eliminated primarily by renal clearance are cisplatin and MTX. Cisplatin is a platinum agent used in bladder and testicular cancer. When co-administered with NSAIDs, the NSAIDs can cause renal insufficiency and have lethal effects [14]. MTX is an antifolate analogue used in leukemia and breast cancer treatment. Subtherapeutic levels of MTX have been identified when co-administered with bicarbonate, because bicarbonate increases urine pH, which leads to increased MTX clearance [15].

Other sources of pharmacokinetic variability

■ Age

All four components of drug disposition (absorption, distribution, metabolism and excretion) are affected by age. Since there is an 11-fold greater incidence of cancer in individuals of more than 65 years of age and more than 60% of all diagnosed cancers are found in individuals in this older age group, this makes age-dependent drug disposition of fundamental importance [16]. Age-related changes in chemotherapeutic drug absorption include reduced gastric acid secretion, reduced gastrointestinal motility and reduced splanchnic blood flow in patients with increased age [17–19]. Changes in distribution can also result from an increased proportionality of body fat, reduced intracellular water or reduced plasma albumin [20–22]. Metabolic changes with age include a reduction of 20–50% of liver mass in patients of 80 years of age or older and up to a 30% reduction of CYP450 activity in patients over the age of 70 when compared with patients in the

20–29-year age group [23,24]. Changes to drug excretion in older individuals include reduced hepatic blood flow and a glomerular filtration rate (GFR) reduction of 1 ml/min per year over the age of 40 [20–22]. Age-related changes drastically affect the pharmacokinetics of drug disposition and should be taken into account in chemotherapy treatments.

■ Polypharmacy

The co-administration of drugs can also affect the four major components of drug disposition. Polypharmacy effects are vast and include changes in absorption, distribution, metabolism and elimination. One example of polypharmacy influencing pharmacokinetics is with the study of tamoxifen, a breast cancer chemotherapy agent, when concomitantly used with selective serotonin reuptake inhibitor antidepressants. In a study of 80 breast cancer patients, the mean plasma concentration of endoxifen, an active metabolite of tamoxifen, was decreased by 56% with co-administration of the selective serotonin-reuptake inhibitor paroxetine [25].

Chemotherapy dosing

■ Body surface area

Cytotoxic chemotherapy is characterized by significant variability in toxic and therapeutic effects. In an attempt to reduce this variability due to interindividual pharmacokinetic differences, chemotherapy doses are individualized according to a patient's BSA. The concept was based on studies that established that the basal metabolic rate varied among species as a function of a power less than 1 (–0.075) of weight, which corresponds to the variation of BSA as a function of weight [26]. The original formula based on length and weight was developed by Du Bois and Du Bois in 1916 and was applied to clinical pharmacology in the 1950s to predict safe starting doses in Phase I clinical trials [26]. Shortly thereafter, the formula was adopted for dose calculation of cytotoxic drugs. Below is one of the most commonly used formulas for BSA:

$$BSA(m^2) = 0.007184 \times (\text{height})^{0.725} \times (\text{weight})^{0.425}$$

The advantages of using this method include a simple and easy-to-use formula and early studies have statistically correlated the BSA with pharmacokinetics (docetaxel and paclitaxel) [27,28]. It should be noted that another study by Rudek *et al.* has shown that BSA does not sufficiently correct for variability in docetaxel [29].

Conversely, the pharmacokinetic parameters of many other chemotherapeutic agents do not correlate with BSA and BSA dosing has failed to produce consistent systemic drug exposure [1]. In clinical practice it is more common to reduce doses in response to adverse effects than to increase dose intensity when the therapy is well tolerated. This can be explained by the fact that it is easy to recognize toxic levels but it is difficult to detect subtherapeutic levels. For example, trials of adjuvant cyclophosphamide, doxorubicin and 5-fluorouracil in breast cancer have shown that underdosing may lead to an almost 20% relative reduction in disease-free survival [1,30–36].

■ TDM & pharmacokinetics-based dosing

A priori method

A priori methods allow the estimation of the dose necessary to reach a target exposure in a given patient using morphological, biological and physiological data such as body weight, age, gender, serum creatinine level and GFR [37]. The dosing of carboplatin by Calvert's and Chatelut's formulas provides an important example of how individual dose estimation is determined using the *a priori* method. Calvert's formula calculates a target AUC between 3 and 8 mg/ml using GFR [38]. Conversely, Chatelut's formula was developed using pharmacokinetic modeling that requires age, gender, weight and serum creatinine levels [39]. Although *a priori* methods account for some interindividual pharmacokinetic variability, their performance is not as good as that of *a posteriori* methods because there is a typical variability of 20% [37].

Test-dose method

The test-dose method is composed of two steps [37]:

- The individual pharmacokinetic parameters are determined after a bolus injection of a moderate dose;
- The parameters are used to calculate the full dose necessary to achieve the target exposure.

This method has been used for MTX owing to the frequent dose adjustments necessary to accommodate the significant interindividual pharmacokinetic differences observed with this drug [40,41]. Use of this approach to chemotherapeutic dosing requires that the drugs have linear pharmacokinetics and may require additional blood samples to determine pharmacokinetic patterns before efficient treatments are begun.

A posteriori methods

Nomograms

A nomogram is a graphical calculating tool with a 2D diagram designed to allow the approximate graphical computation of a function. They have been routinely used for dose adjustments of 5-FU, with the x-axis representing the observed AUC (0–48 h) values and the y-axis representing the percentage of decrease in dose needed to reach the targeted AUC. In one study, 5-FU dose adjustments using the nomogram method were used in a population of patients with head and neck carcinoma. The study showed that by using nomograms for 5-FU, the patients were getting similar therapeutic response rates and reduced toxicities while being administered a lower mean dose [42].

Multilinear regression

Multilinear regression models describe the relationship between exposure-variable AUC values at different time points by using two to three blood samples collected at specified intervals. The exposure-variable AUC is a linear function of the concentration of drug measured at particular time points. This method has been proposed for monitoring AUCs of etoposide, doxorubicin, carboplatin, cyclophosphamide, topotecan, irinotecan and chemotherapeutic metabolites. However, it has not shown sufficient precision for use as a TDM approach [43–52] and is not considered viable with clinical practice owing to the requirement for precise blood sampling, which is difficult to achieve in routine clinical practice.

Bayesian method

The Bayesian estimation method for dose individualization requires a pharmacokinetic population model and a few concentration data points collected after or during administration of the drug. It is a one-stage method where data observed in all patients are considered as a whole, so that it is possible to scatter the different sampling times amongst several patients. The Bayesian method assumes that each patient is a member of a specific population defined by the values intrinsic to the population. This allows for the possibility of having only one blood sampling per patient, compared with multiple sampling with other methods, and thus provides the flexibility to accommodate the few data points at suboptimal time points that may be seen in some clinical settings [37].

One of the most frequently used Bayesian methods is the nonlinear mixed effect model. With this model, interindividual pharmacokinetic variability can be partly explained by

KEY TERM

Immunoassay: Method of analysis using antibodies to selectively bind and quantitate the analyte of interest

individual factors (covariates) such as age, gender or weight [37]. This method provides information on which covariates are used in determining the pharmacokinetics of the drug and how much variability can be explained by them. Bayesian estimation has been used in TDM for 30 years, but only a few of these models have been used in clinical trials or routine practice of chemotherapeutic agents. These agents include MTX [53,54], carboplatin [55–58] and suramin [59,60]. In addition, Bayesian estimators have been developed for cisplatin, etoposide, teniposide, doxorubicin, pirarubicin, irinotecan, paclitaxel, topotecan, vincristine and vinorelbine [37]. With the use of Bayesian dose adjustments, fewer toxic effects were reported. Major advantages and disadvantages of a Bayesian modeling approach are listed in **Box 2**.

Current & prospective use of TDM in chemotherapy agents

■ Current TDM

Methotrexate

Methotrexate is a folic acid antagonist that inhibits DNA, RNA and protein synthesis in proliferating cells and is widely used in the treatment of leukemias and lymphomas. Most notably, a relationship between MTX treatment and efficacy has been established in acute lymphoblastic leukemia (ALL). In 1998, Evans *et al.* reported that pediatric ALL patients that were treated with individually adjusted doses of MTX had significantly better outcomes than those given a fixed dose [61]. Before being adopted as an oncology treatment, MTX was used in low

doses for the treatment of autoimmune diseases, including rheumatoid arthritis, psoriasis and Crohn's disease.

Therapeutic monitoring of MTX drug concentrations is a common practice due to the high interpatient variability of pharmacokinetics, efficacy and toxicity. Additionally, MTX blood concentrations are directly related to observed pharmacological effects. Both the mechanism of action and reported drug toxicities are dependent upon the MTX dosing regimen used (low- or high-dose). Monitoring high-dose therapies is particularly desired, due to the increased costs and toxicities associated with this dosing regimen. Efficacy of MTX dosing is widely variable due to differences in cancer cell sensitivities to the drug [62]. In fact, tumor cells are occasionally reported to demonstrate resistance to MTX, thus drug monitoring may help confirm whether therapeutic levels have been reached in these patients. Another unique feature of MTX that makes monitoring drug concentrations beneficial is the ability to reverse the action of the drug with folinic acid (leucovorin). Monitoring plasma concentrations allows for individualized leucovorin rescue therapies; when toxic MTX levels are reached, leucovorin treatment 'rescues' bone marrow and intestinal epithelial cells by allowing them to resume DNA replication.

As mentioned previously, the test-dose method is frequently employed for monitoring MTX therapies in oncology patients. Serum or plasma concentrations are commonly monitored every 24 h for a period of 3 days [63]; however, several different infusion protocols exist. Bayesian methods have also been used to not only monitor dosing strategies, but also to monitor leucovorin rescue therapy [64]. **Immunoassay** techniques have routinely been used for detecting MTX concentrations, although chromatographic assays have recently been developed [65].

Busulfan

Busulfan is an alkylating agent primarily used for the treatment of chronic myelogenous leukemia (CML), often in high doses as a conditioning agent prior to bone marrow or hematopoietic stem cell transplantation. Alkylation of DNA by busulfan specifically targets proliferating myeloid cells. For myeloablative purposes, busulfan is often co-administered with cyclophosphamide. Both oral and intravenous busulfan are commonly dosed by body weight (mg/kg). Plasma busulfan concentrations are routinely monitored in high-dose patients (16 mg/kg) due to

Box 2. Advantages and disadvantages of Bayesian modeling.

Advantages

- It is possible to visually check modeling efficiency by looking at the concordance between the measured concentration and the predicted concentration time curve.
- Estimation of several pharmacokinetic parameter values and exposure indices simultaneously.
- Flexibility with respect to sampling times, rendering this method more relevant to the constraints of clinical development.
- Inclusion of new data in the population database allows progressive refinement of the population pharmacokinetic mode.

Disadvantages

- Estimator is difficult to develop.

the well-documented inter- and intra-individual pharmacokinetic variation, narrow therapeutic index and direct relationship between exposure and outcome [66–68]. Children in particular exhibit a high degree of busulfan pharmacokinetic variation, with differences documented in age, disease and dosing regimens [66,69–71]. Population pharmacokinetic modeling has also confirmed the wide interpatient variability that is observed in pediatric patients [72]. Toxicities associated with busulfan use include veno-occlusive disease, neurological disorders, pancytopenia and, more rarely, interstitial pulmonary fibrosis ('busulfan lung') [63,67]. Newer therapies commonly incorporate imatinib in place of busulfan in order to reduce these associated toxicities [73].

Therapeutic drug monitoring of busulfan concentrations is commonly achieved by reporting AUC or steady state concentrations (C_{ss}). Owing to differences in routes of administration and dosing intervals, several samples are needed to establish the pharmacokinetic pattern of busulfan therapies. Obtaining seven or 12 points of measurement throughout a preliminary drug course provides a concentration–dose curve that aids clinicians in patient-specific dose adjustments. Limited sampling models aim to use as few as two to four drug concentrations to monitor therapy, in order to decrease the time-consuming and complex nature of monitoring this drug [74–76]. However, although these approaches limit the number of blood draws required from each patient, the timing of each draw is critical to final calculations and the utility of these models in specific patient groups must still be evaluated. The use of Bayesian pharmacokinetic modeling has been reported to reduce toxicity and mortality in pediatric bone marrow and hematopoietic stem cell-transplant patients [74,77–79].

Busulfan concentrations can be monitored in serum, plasma and cerebrospinal fluid by chromatography with and without MS or by immunoassay methods [63,80]. ELISA formats have also recently been adapted to detect busulfan [81]. Newer LC and MS/MS methods to detect busulfan concentrations in oral fluids have recently been described [69]. Use of this noninvasive sample type aims to alleviate the risk and inconvenience of multiple blood draws for monitoring therapies.

Azathioprine

The thiopurine agent azathioprine has been used as an immunosuppressant for a wide range of diseases, including multiple sclerosis,

rheumatoid arthritis, inflammatory bowel disease and also for transplantation. Azathioprine, acting as a prodrug, and its main metabolite, 6-mercaptopurine (MP), are also used for the treatment of lymphomas and childhood ALL. Both drugs act by inhibiting purine metabolism and, thus, DNA synthesis, in proliferating lymphocytes. Azathioprine and 6-MP pharmacokinetics and the formation of cytotoxic metabolites can vary considerably between patients. Absorption of azathioprine is necessary to exert the effects of the inactive prodrug, and the inactivation of 6-MP by thiopurine methyltransferase is highly polymorphic between individuals [82]. Population studies of xanthine oxidase, an important metabolizer of MP, have shown a four- to ten-fold interindividual variation [83]. A decreased level of xanthine oxidase potentiates the cytotoxic effects of MP, as seen by the co-administration of the xanthine oxidase inhibitor allopurinol. Due to these variations and the established relationship between 6-MP pharmacokinetics and efficacy, routine monitoring of azathioprine and 6-MP concentrations often help improve dosing strategies in patients [84].

6-mercaptopurine concentrations are quantified to monitor most azathioprine therapies. Alternatively, 6-MP eventually forms 6-thioguanine nucleotides that can also be followed for TDM. Thiopurine methyltransferase activity in red blood cells can also be determined to predict whether an individual patient is at risk for excessive myelosuppression after exposure to thiopurine agents. Drug concentrations can be measured in plasma, urine, red blood cells, neutrophils and lymphocytes using chromatographic methods [85]. Urine concentrations of 6-MP have been correlated with plasma AUC concentrations and may provide a less-invasive alternative to multiple phlebotomies for TDM [86].

Prospective chemotherapy candidates for TDM

■ mTOR inhibitors

Sirolimus, also known as rapamycin, is an immunosuppressant agent originally developed as an antifungal agent. However, this use was abandoned when it was discovered that the drug possessed significant antiproliferative and immunosuppressive properties. Sirolimus, along with its derivative everolimus, comprise a class of drugs known as inhibitors of mTOR. These drugs have primarily been used to prevent rejection in organ transplantation and are now finding increased use in the treatment of some

cancers [87]. Both sirolimus and everolimus are metabolized by CYP3A4, a family of enzymes involved in the metabolism of several immunosuppressive agents used in organ transplant and chemotherapy [88]. The genetic polymorphism of these enzymes and combination of drug therapy can affect plasma concentrations of mTOR and may lead to toxicities or treatment failure [89,90]. Cattaneo *et al.* analyzed 2658 sirolimus trough samples in 495 kidney transplant recipients and found that dose-normalized sirolimus trough concentrations were significantly higher in patients treated with cyclosporine and sirolimus, compared with patients treated with mycophenolate mofetil and sirolimus or with patients treated with steroids and sirolimus [91]. They also showed that mean intra- and interpatient variability was 19 and 47%, respectively. Their study suggests that different immunosuppressants significantly interfere with sirolimus pharmacokinetics and can affect clinical outcomes. Several studies with everolimus have demonstrated the same potential for interindividual variability and drug–drug interactions as seen with sirolimus in a review by Sanchez-Fructuoso [92].

In the context of cancer chemotherapy, the issue is more complicated. There are several studies that demonstrate a favorable response (overall survival, progression-free survival and median time to progression) when mTOR inhibitors are added to existing chemotherapy regimens [93–95]. However, as with many of the other chemotherapeutic agents, there is no definitive correlation between drug exposure and desirable clinical response. There is a well-defined relationship between drug exposure and toxic effects, but the conventional wisdom is that TDM is not necessary and toxic effects can be mitigated through early recognition and prompt intervention to provide supportive measures for the patient [96]. Although TDM of mTOR inhibitors is the standard of care in transplantation, it is not widely implemented – if at all – in the field of clinical oncology, with the exception of monitoring immunosuppression in bone marrow transplant patients [97].

■ 5-flourouracil

5-flourouracil has been used in the treatment of cancer for over 40 years. Its mechanism of action involves the inhibition of thymidylate synthase which blocks the synthesis of pyrimidine thymidine, a nucleotide required for DNA replication. 5-FU effects are seen in rapidly dividing cancer cells that rely heavily on nucleotide synthesis.

It has principally been used in the treatment of colorectal cancer and pancreatic cancer since 1978 [98]. One source of variability in patient response is a functional variant of dihydropyrimidine dehydrogenase (DPD) resulting in deficiency of that enzyme; DPD is responsible for the degradation of 80–90% of 5-FU. A total of 19 DPD variant alleles have been identified with decreased enzyme activity, one of which is a point mutation resulting in a truncated protein with reduced activity [99]. In addition, pharmacokinetic variability can account for variation in patient response. Recent studies have shown that the current standard approach for calculating treatment doses of 5-FU is not effective in achieving optimal plasma concentration. The standard BSA-based dosing is associated with up to 100-fold plasma 5-FU variability and is a major contributor to treatment toxicity and treatment failure. Two studies exemplify the limited utility of 5-FU dosing based on BSA. The first is a study by Gamelin *et al.*, where the authors established a lack of association between BSA and 5-FU clearance in 81 patients with metastatic colorectal cancer [100]. The second study by Milano *et al.* showed a similar lack of association between BSA and 5-FU clearance in a study of 380 patients with head and neck cancer [101].

Clinical studies in the past 20 years have demonstrated reduced toxicity and improved clinical outcomes with pharmacokinetic dose management. These studies have identified an optimal target therapeutic range and formulated dose-adjustment algorithms for optimal plasma concentration ranges [98]. Direct monitoring of 5-FU may be a more rational approach compared with the standard approach and would aid in achieving optimal systemic drug exposure in a more personalized manner. One of the most recent studies of 208 patients with metastatic colorectal cancer by Gamelin *et al.* demonstrated a response rate of 18.3% and an overall survival of 16 months using BSA dosing, while a response rate of 33.7% and an overall survival of 22 months using pharmacokinetically guided dosing. They concluded that individual FU dose adjustment, based on pharmacokinetic monitoring, resulted in improved objective response rates, a higher survival rate and fewer toxicities [102].

■ Imatinib

Imatinib is a chemotherapeutic agent used in the treatment of CML and gastrointestinal stromal tumors (GISTs). It is a 2-phenylaminopyrimidine

derivative that functions as a specific inhibitor of many tyrosine kinase enzymes by occupying the tyrosine kinase active site, leading to a decrease in enzyme activity. In patients with CML, a clonal myeloproliferative disorder of hematopoietic stem cells, a cytogenetic presence of the Philadelphia (Ph) chromosome t(9,22)(q34;q11) occurs in 90–95% of patients. The formation of the Ph chromosome results from the *ABL* proto-oncogene being translocated from chromosome 9 to the *BCR* gene located in chromosome 22. The resultant fusion gene, *BCR-ABL*, transcribes a chimeric 8.5 mRNA that translates into a protein denoted as p210. This protein increases tyrosine kinase activity and transforms normal hematopoietic cells into CML cells [103,104]. Imatinib acts by binding to the ATP binding pocket of the *BCR-ABL* fusion chimeric protein, causing a stabilization of the inactive form of *BCR-ABL* [105]. Treatment with imatinib results in a complete hematological remission rate of more than 95% and a major cytogenetic response rate of more than 80% in newly diagnosed CML patients [106].

Studies of imatinib's pharmacokinetic have shown high bioavailability of 98% when administered orally [106]. In the systemic circulation, it is 95% bound to plasma protein albumin and α -1 AAG. It is primarily metabolized in the liver by several isoenzymes of the CYP450 system, including CYP3A4 and, to a lesser extent, CYP1A2, CYP2D6, CYP2C9 and CYP2C19 [107]. It is eliminated predominantly by fecal excretion (68%) and in urine (13%) [106]. Several factors have been proposed as determinants of suboptimal concentration of imatinib in patients undergoing oral imatinib therapy, including baseline presence of *BCR-ABL* mutations [108,109], interindividual variability of metabolizing enzymes (CYP system) [110,111] and variability in efflux and uptake transporter activities [112].

The standard recommended dose is 400 mg daily in the chronic phase and 600 mg in the accelerated phase or blast crisis [105]. The mean plasma trough C_{ss} 24 h after administration of 400 mg of imatinib is 1.46 μ M/l [113]. However, despite adequate dosing, not all patients in the chronic phase of CML achieve cytogenetic responses (cytogenetic response is defined by the percentage of Ph chromosome identified during metaphase in bone marrow). A study by Larson *et al.* reported that the reason for poor therapeutic response in some patients was the interindividual variation in plasma levels of imatinib [107]. In addition,

Druker *et al.* [113] and Peng *et al.* [114] reported that a complete hematological response was achieved when plasma imatinib levels were higher than 1 μ M. A recent study by Singh *et al.* reported mean plasma levels of imatinib in responders were significantly higher than those in nonresponders (2.34 ± 0.52 vs 0.69 ± 0.15 μ M) [106].

Gastrointestinal stromal tumor is the most common mesenchymal tumor of the GI tract with activating mutations of the *KIT* or *PDGRR* genes [115,116]. Imatinib targets the ATP binding site of the tyrosine kinase region in KIT and PDGF receptor-interrupting proliferation and survival signaling pathways within the cell [117,118]. Constitutive activation of c-KIT, associated with various mutation profiles is observed in the majority of GISTs. The most common mutation of the KIT gene is located on exon 11 and is associated with a better response to imatinib when compared with another common mutation in exon 9 [119]. **The exon 9 mutation** occurs in 10–15% of patients and is a subset of GISTs that has an aggressive clinical behavior [120]. Approximately 10% of patients have undetectable mutations (wild-type [wt]) [121]. Widmer *et al.* recently showed that patients harboring a 'sensitive' c-KIT genotype (exon 11 mutation) are exposed to concentrations that are near the top of the concentration–response curve while patients with the 'resistant' genotype (exon 9 mutation) are lying in the steep part of the curve where the concentration–response relationship can be observed. Patients with exon 9 mutations would benefit from adjustment of their imatinib exposure levels owing to the ability to correlated concentration and therapeutic effect [122].

Additionally, interindividual plasma concentration could also be caused by: an increase in cellular efflux of imatinib by P-gp transporter [122], a decrease in cellular influx mediated by the uptake carrier organic cation transporter (hOCT1) [123], modulation of imatinib binding to α 1-binding glycoprotein in plasma [119] and enhanced drug metabolism [124]. A given dose therefore yields very different circulating concentrations between patients, as shown in data by Larson *et al.* [107]. Demtri *et al.* also recently correlated that in patients with advanced GIST, IM trough levels at steady state were associated with clinical benefit and patients with imatinib C_{min} below 1100 ng/ml showed a shorter time to progression and lower rate of clinical benefit [119]. These findings suggest that the plasma levels of imatinib affect response to therapy and TDM should be used to check optimal therapeutic levels

in routine clinical practice. Another interesting study demonstrated that everolimus administered in combination with imatinib shifts the equilibrium of imatinib between red blood cells and plasma toward the red blood cells, such that plasma availability is reduced [125].

■ EGF receptor inhibitors

The EGF receptor (EGFR) is a cell surface receptor for members of the EGF family of extracellular protein ligands. It acts as a tyrosine kinase receptor, triggering complex intracellular signaling cascades. Mutations involving EGFR often lead to constant activation, which then results in uncontrolled cell division and a predisposition for cancer [126]. Mutations that lead to EGFR overexpression, known as upregulation or overactivity, have been associated with a number of cancers, including lung, pancreatic, colorectal and head and neck cancers. Consequently, EGFR is the target of an expanding class of anti-cancer therapies. Some examples are gefitinib for lung cancer, erlotinib for lung and pancreatic cancer and cetuximab for colon, head and neck cancers. The pharmacokinetics of these three agents are discussed below.

Gefitinib is a drug that inhibits EGFR tyrosine kinase by binding to the ATP binding site of the enzyme, thus blocking the RAS signaling transduction cascade in the EGFR tyrosine kinase pathway. It is a lipophilic dibasic compound with two pKa values of 5.28 and 7.14 and exhibits a pH-dependent solubility in gastrointestinal fluid. The solubility of gefitinib in aspirated human gastric fluid at pH 5.0 is 4.98 gm/ml and in aspirated intestinal fluid at pH 7.0 is 0.085 mg/ml [127]. Due to its dibasic properties, studies have shown that changes in the gastric pH levels alter the oral bioavailability of gefitinib [128]. Gefitinib is extensively distributed in the body and is mainly eliminated as a metabolite [129]. A dose of 250 mg of gefitinib has a variable plasma half-life of 39.7 h with a range between 26.9–83.2 h [128]. A recent study by Wilson *et al.* reported that interindividual differences in plasma exposure to gefitinib is likely multifactorial and may include low jejunal pH, increased expression of enzymatic and transporter activity and rapid small intestine transit [130].

Erlotinib is an orally active EGFR tyrosine kinase inhibitor that blocks EGFR-mediated intracellular signaling and arrests cell-cycle progression in the G1 phase [131]. Erlotinib is indicated for the treatment of patients with locally advanced or metastatic non-small-cell

lung cancer after failure of at least one prior chemotherapy regimen and is approved for use in combination with gemcitabine chemotherapy for treatment of locally advanced, inoperable or metastatic pancreatic cancer [132]. Erlotinib is extensively metabolized by hepatic enzymes CYP3A4 and CYP1A2 and to a lesser degree by the extrahepatic enzyme CYP3A4 in the intestine, CYP1A1 in the lung and CYP1B1 in tumor tissues [133]. It is 95% protein bound in plasma and has a clearance of 6.3 l/h and a volume of distribution of 136.4 l. It has a highly variable C_{ss} of 1200 ± 620 ng/ml and a mean half-life of 24.4 ± 14.6 h [134]. Lu *et al.* studied 1047 patients receiving erlotinib with non-small-cell lung cancer to assess the pharmacokinetics of erlotinib in a large patient population and reported total bilirubin, α 1-AAG and smoking status as the most critical factors explaining interindividual variability for erlotinib clearance [134]. This population pharmacokinetic model predicts that patients with a high concentration (95th percentile) of AAG (2.3 g/l) or total bilirubin (1.1 mg/ml) would have erlotinib clearance decrease by 31 and 30%, respectively. Furthering Lu's paper, Thomas *et al.*, used population pharmacokinetics in patients with squamous cell carcinoma to reported patient age, hepatic function, ABCG2 genetic polymorphism and smoking status to contribute to the high interindividual variability in erlotinib pharmacokinetics [135].

■ Platinum-based agents

Cisplatin is a platinum-based chemotherapy drug widely used to treat various types of solid tumors, including sarcomas, small-cell carcinoma, ovarian cancer, lymphomas and germ cell tumors. Owing to the strong pharmacokinetic relationship between dose and therapeutic response, dose intensity is important to achieve optimal therapeutic response. Early studies have shown that free cisplatin clearance is related to patient's BSA, therefore dosage is mostly adjusted using the *a priori* method, with BSA as the single parameter [136,137]. Using this approach, later studies have shown mixed results for accurately predicting cisplatin exposure and toxicities based on BSA [138]. By using Bayesian adaptive dosing instead of BSA, Salas *et al.* were able to achieve C_{max} target levels with an overall precision of 6.6% despite high interpatient variability (54%) described with cisplatin pharmacokinetics [138]. Their method also allowed 20% higher doses than the ones commonly recommended in the literature and with decreased toxicities [138].

Carboplatin is a platinum-based chemotherapy agent that was introduced for the treatment of patients with favorable prognosis testicular teratoma. Cisplatin-based chemotherapy such as bleomycin and vinblastine has over a 90% complete remission rate for patients with good prognosis, but patients are often plagued with acute toxicity, including nausea and vomiting. Of even greater concern is the chronic nephrotoxicity, neurotoxicity and ototoxicity associated with these chemotherapy agents [38].

Carboplatin's major route of elimination is via the kidney, thus inadequate renal function can lead to toxic or subtherapeutic concentrations. Due to the decrease in toxicities noted in carboplatin treatment in prior studies using *a priori* estimation, further studies of carboplatin by Harland *et al.* and Egorin *et al.* reported that dosing of carboplatin should not be based on BSA but rather on a simple formula that accounts for pharmacokinetic contribution of renal excretion (24 h creatinine clearance) [139,140]. Several formulas based on *a priori* determination have followed, including Calvert's, Chatelut, Sanaka, Schwartz and Cockcroft–Gault equations; the most widely used method to calculate an individual dose of carboplatin is a modified Cockcroft–Gault equation:

$$(140 - \text{age}) \times \left(\frac{\text{actual weight}}{72 \times \text{serum creatinine}} \right)$$

Implementation of these formulas for calculation of individualizing doses of carboplatin has reduced pharmacokinetic variability and has led to dosing of carboplatin being based on pharmacokinetics rather than BSA. Four other studies applying a Bayesian estimation method to individualized dosing have reported a significantly decreased variation in carboplatin exposure as result of TDM, compared with the standard dose [56,58,141,142].

■ Etoposide

Etoposide phosphate is a topoisomerase II inhibitor that is used in the treatment of malignancies such as Ewing's sarcoma, testicular cancer, lymphoma, nonlymphocytic leukemia, glioblastoma multiforme and small-cell carcinoma of the lung. Traditionally, dosing is based on BSA and administered over 3–5 days. However, Nguyen *et al.* studied the population pharmacokinetics of etoposide and concluded that interindividual variability was important in the treatment of small-cell lung cancer patients and that doses should be adjusted based on serum

creatinine level [143]. Supporting Nguyen's findings, a study of 52 patients with small-cell lung cancer using population pharmacokinetics showed no relationship between BSA and etoposide clearance, but concluded that there was a significant relationship between etoposide clearance and kidney function (serum creatinine) [144]. In addition, the authors reported a significant reduction (median AUC: 260 vs 339 mg·h/l) of systemic exposure of etoposide secondary to the 28% increase (median CL: 2.42 vs 1.89 l/h; $p < 0.0005$) in clearance when ifosfamide was coadministered.

■ Doxorubicin

Doxorubicin is an anthracycline antibiotic that is widely used in the treatment of a variety of cancers, including hematological malignancies, soft-tissue sarcomas and many types of carcinomas. It functions by intercalating with DNA and, thus, inducing apoptosis of cancer cells. There have been very few studies of the relationship between doxorubicin pharmacokinetics and clinical response. A recent study of doxorubicin by Elis *et al.* studied the association of doxorubicin pharmacokinetics with remission rates in Hodgkins lymphoma patients [145]. They demonstrated that successful remission was associated with a higher median AUC. Those with median serum concentration of 280 ng/ml obtained successful remission compared with those who failed remission with median concentration of 73 ng/ml [145]. The authors concluded that TDM of doxorubicin may be warranted in patients with Hodgkins lymphoma, due to the wide variability observed in interindividual pharmacokinetics.

■ Suramin

Suramin is an aromatic polysulfonated compound that has been evaluated as a chemotherapy agent in prostate cancer. Studies have shown that suramin has a concentration-dependent effect on prostate cancer (TABLE 1) [146]. In addition, studies using maximal tolerated dosing have demonstrated suramin plasma concentrations of 100–200 µM and half-lives ranging between

Table 1. Suramin concentration dependency[†].

Concentration	Effect
<50 µM	Inhibits reverse transcriptase, protein kinase C, TGF-β, basic FGF and RNA polymerase
>50 µM	Inhibits IL-2, IGF 1, topoisomerase 2, EGF and TNF
>100 µM	Cytotoxicity

[†]The biological effects of suramin are dependent upon the concentration administered.

30 and 50 days. The unusually long half-life of suramin increases the probability of drug accumulation and this, coupled with significant toxic effects, have led to population-based pharmacokinetic studies that recommended a fixed dosing schedule with plasma drug concentrations maintained between 70 and 200 μM [146].

Additional studies of suramin have reported that suramin concentrations between 10 and 50 μM significantly enhanced the therapeutic efficacy of chemotherapy doxorubicin, paclitaxel, docetaxel and mitomycin without increased toxicity when used to treat subcutaneous or metastatic human xenograft tumors of breast, prostate and bladder in immunodeficient mice [146]. A recent study of suramin dosing using nomograms based on population pharmacokinetics reported successful delivery to target concentrations of suramin in greater than 95% of the treatments [147].

Conclusion & future perspective

Advances in the field of oncology have led to the development of many new chemotherapy agents, but to effectively and safely use these drugs we must take into account the wide pharmacokinetic variability that exists in a diverse population. From the initial oral absorption of a drug to the final elimination from the body, there are many sources of pharmacokinetic variability that can cause underdosing and treatment failure to overdosing and toxic buildup. The current approach to chemotherapy treatments by using BSA-based dosing does not take into account the wide interpatient pharmacokinetic variability and is not optimum for the treatment of cancer, yet there has been no substantial change in clinical practice. Minimizing interpatient variability using pharmacokinetically guided dosage may reduce the probability of toxic effects and treatment failures. Treatment failure reduces the chances of long-term disease-free survival for cancer patients and successful first time chemotherapy treatment is of particular importance in childhood ALL. It has been shown that treatment failure and subsequent intensive second remission therapy carries the risk of secondary malignancies [148].

Any argument for the replacement of BSA-based dosing must propose a better alternative. While it is hoped that the design of new agents will lead to increased success in the treatment of cancers while minimizing toxicity, it is essential that we use the drugs currently available to their maximum potential. For drugs in clinical

use, studies using population-based approaches to identify factors with predictive value for drug pharmacokinetic and therapeutic effect are clearly valuable, as shown in our discussion. The majority of prospective dose-adaptation studies for chemotherapeutic agents have shown positive results when pharmacokinetically guided dose adaptation have resulted in desired systemic exposure. These types of studies often report tight control of plasma concentration levels, especially when using the Bayesian approach. However, few studies have evaluated tumor response and toxicity profiles in the context of TDM by randomized comparative trials. The obstacles to these types of trials are significant. Funding these trials is difficult because Phase III randomized control trials are expensive and will be competing with other trials investigating newer 'blockbuster'-type treatments for resources. In addition, they require a large number of patients and the number of patients willing to enroll in clinical trials is limited – there will be competition with other trials for patient enrollment as well. Drug regimens are constantly changing as clinicians/scientists are investigating different combinations of therapeutic agents. Lastly, for most chemotherapeutic drugs, there is no widely available assay for monitoring patients. In most, if not all, the pharmacokinetic and TDM studies, drug measurements have been made using HPLC or LC-MS/MS methods. However, most clinical laboratories do not have access to these methods due to lack of capital resources, technical expertise or both. Automated immunoassays are a preferred method for clinical laboratories, but are costly to develop and present their own technical challenges in the form of crossreactivity with drug metabolites and structural analogues, as well as heterophilic antibody interferences. Development of commercial assays will be dependent on defining the clinical need for TDM assays in this field.

In the future, it will be important to find ways to gather data to investigate the potential benefits of TDM in oncology patients. It is equally important for investigators and/or *in vitro* diagnostics companies to develop robust, easily accessible assays for the measurement of chemotherapeutic agents in blood. Last and most importantly, it will take a large-scale collaborative effort between oncologists, pharmacists and laboratorians to move from empiric treatment of cancer to a more rational approach to drug delivery, based on drug concentrations and other clinical biomarkers.

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Executive summary**Pharmacokinetics**

- One significant source of interindividual variability in chemotherapy is due to differences in patient pharmacokinetics.
- Pharmacokinetic variability comes from a variety of sources, including drug absorption, distribution, metabolism and clearance.
- Patient pharmacokinetics also vary with age and the addition of other pharmaceutical agents.

Chemotherapy dosing

- The typical method for minimizing interindividual variability in pharmacokinetics is to normalize dosing to patient body surface area.
- In many cases, body surface area-based dosing does not acceptably reduce variability.
- Pharmacokinetics-based dosing includes both *a priori* and *a posteriori* methods for dose individualization.

Current therapeutic drug monitoring in cancer chemotherapy

- There are only three drugs that are monitored with any regularity in cancer chemotherapy: methotrexate, busulfan and azathioprine.

Prospective chemotherapy candidates for therapeutic drug monitoring

- There are several drugs that have demonstrated significant pharmacokinetic variability that may be candidates for therapeutic drug monitoring, including mTOR inhibitors, 5-fluorouracil, imatinib, EGF receptor inhibitors, platinum-based agents, etoposide, doxorubicin and suramin.
- Establishing therapeutic drug monitoring protocols for these agents, and others, is difficult because, for most chemotherapy agents, there is no defined relationship between blood concentration and clinical efficacy.

Bibliography

Papers of special note have been highlighted as:
▪ of interest

- 1 Veal GJ, Coulthard SA, Boddy AV. Chemotherapy individualization. *Invest. New Drugs* 21(2), 149–156 (2003).
- 2 Hon YY, Evans WE. Making TDM work to optimize cancer chemotherapy: a multidisciplinary team approach. *Clin. Chem.* 44(2), 388–400 (1998).
- Describes the approach needed for therapeutic drug monitoring (TDM) to make an impact in chemotherapy management.
- 3 Moyer TP, McMillin GA. Therapeutic drugs. In: *Teitz Fundamentals of Clinical Chemistry*. Burtis CA, Ashwood ER, Bruns DE (Eds). Saunders Elsevier, MO, USA, 539–561 (2008).
- 4 Undevia SD, Gomez-Abuin G, Ratain MJ. Pharmacokinetic variability of anticancer agents. *Nat. Rev. Cancer* 5(6), 447–458 (2005).
- Excellent review of pharmacokinetic variability in chemotherapeutic drugs.
- 5 Slaviero KA, Clarke SJ, Rivory LP. Inflammatory response: an unrecognized source of variability in the pharmacokinetics and pharmacodynamics of cancer chemotherapy. *Lancet Oncol.* 4(4), 224–232 (2003).
- 6 Nozawa T, Minami H, Sugiura S, Tsuji A, Tamai I. Role of organic anion transporter OATP1B1 (OATP-C) in hepatic uptake of irinotecan and its active metabolite, 7-ethyl-10-hydroxycamptothecin: *in vitro* evidence and effect of single nucleotide polymorphisms. *Drug Metab. Dispos.* 33(3), 434–439 (2005).
- 7 Baker SD, van Schaik RH, Rivory LP *et al.* Factors affecting cytochrome P450 3A activity in cancer patients. *Clin. Cancer Res.* 10(24), 8341–8350 (2004).
- 8 Williams ML, Bhargava P, Cherrouk I, Marshall JL, Flockhart DA, Wainer IW. A discordance of the cytochrome P450 2C19 genotype and phenotype in patients with advanced cancer. *Br. J. Clin. Pharmacol.* 49(5), 485–488 (2000).
- 9 Beutler E, Gelbart T, Demina A. Racial variability in the UDP-glucuronosyltransferase 1 (UGT1A1) promoter: a balanced polymorphism for regulation of bilirubin metabolism? *Proc. Natl Acad. Sci. USA* 95(14), 8170–8174 (1998).
- 10 Innocenti F, Undevia SD, Iyer L *et al.* Genetic variants in the UDP-glucuronosyltransferase 1a1 gene predict the risk of severe neutropenia of irinotecan. *J. Clin. Oncol.* 22(8), 1382–1388 (2004).
- 11 Han JY, Lim HS, Yoo YK *et al.* Associations of ABCB1, ABCC2, and ABCG2 polymorphisms with irinotecan-pharmacokinetics and clinical outcome in patients with advanced non-small cell lung cancer. *Cancer* 110(1), 138–147 (2007).
- 12 Branch RA, Herbert CM, Read AE. Determinants of serum antipyrine half-lives in patients with liver disease. *Gut* 14(7), 569–573 (1973).
- 13 Ratain MJ, Vogelzang NJ, Sinkule JA. Interpatient and inpatient variability in vinblastine pharmacokinetics. *Clin. Pharmacol. Ther.* 41(1), 61–67 (1987).
- 14 Balis FM. Pharmacokinetic drug interactions of commonly used anticancer drugs. *Clin. Pharmacokinet.* 11(3), 223–235 (1986).
- 15 Lippens RJ. Methotrexate. I. Pharmacology and pharmacokinetics. *Am. J. Pediatr. Hematol. Oncol.* 6(4), 379–395 (1984).
- 16 Yancik R. Cancer burden in the aged: an epidemiologic and demographic overview. *Cancer* 80(7), 1273–1283 (1997).
- 17 Iber FL, Murphy PA, Connor ES. Age-related changes in the gastrointestinal system. Effects on drug therapy. *Drugs Aging* 5(1), 34–48 (1994).
- 18 Corcoran ME. Polypharmacy in the older patient with cancer. *Cancer Control* 4(5), 419–428 (1997).

- 19 Skirvin JA, Lichtman SM. Pharmacokinetic considerations of oral chemotherapy in elderly patients with cancer. *Drugs Aging* 19(1), 25–42 (2002).
- 20 Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. *N. Engl. J. Med.* 307(11), 652–659 (1982).
- 21 Anderson S, Brenner BM. Effects of aging on the renal glomerulus. *Am. J. Med.* 80(3), 435–442 (1986).
- 22 Lichtman SM, Schulman P, Budman DR. Erythroleukemia in the adjuvant treatment of breast cancer. *NY State J. Med.* 85(10), 601–603 (1985).
- 23 Sotaniemi EA, Arranto AJ, Pelkonen O, Pasanen M. Age and cytochrome P450-linked drug metabolism in humans: an analysis of 226 subjects with equal histopathologic conditions. *Clin. Pharmacol. Ther.* 61(3), 331–339 (1997).
- 24 Vestal RE. Aging and pharmacology. *Cancer* 80(7), 1302–1310 (1997).
- 25 Jin Y, Desta Z, Stearns V *et al.* *Cyp2d6* genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. *J. Natl Cancer Inst.* 97(1), 30–39 (2005).
- 26 Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. *Arch. Intern. Med.* 17, 863–871 (1916).
- 27 Bruno R, Vivier N, Vergniol JC, De Phillips SL, Montay G, Sheiner LB. A population pharmacokinetic model for docetaxel (taxotere): model building and validation. *J. Pharmacokinet. Biopharm.* 24(2), 153–172 (1996).
- 28 Smorenburg CH, Sparreboom A, Bontenbal M, Stoter G, Nooter K, Verweij J. Randomized cross-over evaluation of body-surface area-based dosing versus flat-fixed dosing of paclitaxel. *J. Clin. Oncol.* 21(2), 197–202 (2003).
- 29 Rudek MA, Sparreboom A, Garrett-Mayer ES *et al.* Factors affecting pharmacokinetic variability following doxorubicin and docetaxel-based therapy. *Eur. J. Cancer* 40(8), 1170–1178 (2004).
- 30 Felici A, Verweij J, Sparreboom A. Dosing strategies for anticancer drugs: the good, the bad and body-surface area. *Eur. J. Cancer* 38(13), 1677–1684 (2002).
- 31 Gurney H. Dose calculation of anticancer drugs: a review of the current practice and introduction of an alternative. *J. Clin. Oncol.* 14(9), 2590–2611 (1996).
- 32 Egorin MJ. Horseshoes, hand grenades, and body-surface area-based dosing: aiming for a target. *J. Clin. Oncol.* 21(2), 182–183 (2003).
- Excellent discussion of the pitfalls of using body surface area-based dosing.
- 33 Lyman GH, Dale DC, Crawford J. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: a nationwide study of community practices. *J. Clin. Oncol.* 21(24), 4524–4531 (2003).
- 34 de Jonge ME, van den Bongard HJ, Huitema AD *et al.* Bayesian pharmacokinetically guided dosing of paclitaxel in patients with non-small cell lung cancer. *Clin. Cancer Res.* 10(7), 2237–2244 (2004).
- 35 Baker SD, Verweij J, Rowinsky EK *et al.* Role of body surface area in dosing of investigational anticancer agents in adults, 1991–2001. *J. Natl Cancer Inst.* 94(24), 1883–1888 (2002).
- 36 van den Bongard HJ, Mathot RA, Beijnen JH, Schellens JH. Pharmacokinetically guided administration of chemotherapeutic agents. *Clin. Pharmacokinet.* 39(5), 345–367 (2000).
- 37 Alnaim L. Therapeutic drug monitoring of cancer chemotherapy. *J. Oncol. Pharm. Pract.* 13(4), 207–221 (2007).
- 38 Calvert AH, Newell DR, Gumbrell LA *et al.* Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J. Clin. Oncol.* 7(11), 1748–1756 (1989).
- 39 Chatelut E, Canal P, Brunner V *et al.* Prediction of carboplatin clearance from standard morphological and biological patient characteristics. *J. Natl Cancer Inst.* 87(8), 573–580 (1995).
- 40 Graf N, Winkler K, Betlemovic M, Fuchs N, Bode U. Methotrexate pharmacokinetics and prognosis in osteosarcoma. *J. Clin. Oncol.* 12(7), 1443–1451 (1994).
- 41 Pignon T, Lacarelle B, Duffaud F *et al.* Pharmacokinetics of high-dose methotrexate in adult osteogenic sarcoma. *Cancer Chemother. Pharmacol.* 33(5), 420–424 (1994).
- 42 Fety R, Rolland F, Barberi-Heyob M *et al.* Clinical impact of pharmacokinetically-guided dose adaptation of 5-fluorouracil: results from a multicentric randomized trial in patients with locally advanced head and neck carcinomas. *Clin. Cancer Res.* 4(9), 2039–2045 (1998).
- 43 Gallo JM, Laub PB, Rowinsky EK, Grochow LB, Baker SD. Population pharmacokinetic model for topotecan derived from Phase I clinical trials. *J. Clin. Oncol.* 18(12), 2459–2467 (2000).
- 44 Montazeri A, Boucaud M, Lokiec F *et al.* Population pharmacokinetics of topotecan: intraindividual variability in total drug. *Cancer Chemother. Pharmacol.* 46(5), 375–381 (2000).
- 45 Huitema AD, Mathot RA, Tibben MM, Schellens JH, Rodenhuis S, Beijnen JH. Validation of techniques for the prediction of carboplatin exposure: application of Bayesian methods. *Clin. Pharmacol. Ther.* 67(6), 621–630 (2000).
- 46 Minami H, Beijnen JH, Verweij J, Ratain MJ. Limited sampling model for area under the concentration time curve of total topotecan. *Clin. Cancer Res.* 2(1), 43–46 (1996).
- 47 Stromgren AS, Sorensen BT, Jakobsen P, Jakobsen A. A limited sampling method for estimation of the etoposide area under the curve. *Cancer Chemother. Pharmacol.* 32(3), 226–230 (1993).
- 48 Ratain MJ, Robert J, van der Vijgh WJ. Limited sampling models for doxorubicin pharmacokinetics. *J. Clin. Oncol.* 9(5), 871–876 (1991).
- 49 Sorensen BT, Stromgren A, Jakobsen P, Jakobsen A. A limited sampling method for estimation of the carboplatin area under the curve. *Cancer Chemother. Pharmacol.* 31(4), 324–327 (1993).
- 50 Miyazaki M, Fujiwara Y, Takahashi T *et al.* Limited-sampling models for estimation of the carboplatin area under the curve. *AntiCancer Res.* 17(6D), 4571–4575 (1997).
- 51 Egorin MJ, Forrest A, Belani CP, Ratain MJ, Abrams JS, Van Echo DA. A limited sampling strategy for cyclophosphamide pharmacokinetics. *Cancer Res.* 49(11), 3129–3133 (1989).
- 52 Mick R, Gupta E, Vokes EE, Ratain MJ. Limited-sampling models for irinotecan pharmacokinetics–pharmacodynamics: prediction of biliary index and intestinal toxicity. *J. Clin. Oncol.* 14(7), 2012–2019 (1996).
- 53 Schumitzky A. Nonparametric EM algorithms for estimating prior distributions. *App. Math. Comput.* 45, 143–157 (1991).
- 54 Iliadis A, Bachir-Raho M, Bruno R, Favre R. Bayesian estimation and prediction of clearance in high-dose methotrexate infusions. *J. Pharmacokinet. Biopharm.* 13(1), 101–115 (1985).
- 55 Peng B, Boddy AV, Cole M *et al.* Comparison of methods for the estimation of carboplatin pharmacokinetics in paediatric cancer patients. *Eur. J. Cancer* 31A(11), 1804–1810 (1995).
- 56 Johansen MJ, Madden T, Mehra RC *et al.* Phase I pharmacokinetic study of multicycle high-dose carboplatin followed by peripheral-

- blood stem-cell infusion in patients with cancer. *J. Clin. Oncol.* 15(4), 1481–1491 (1997).
- 57 Doz F, Urien S, Chatelut E *et al.* A limited-sampling method for evaluation of the area under the curve of ultrafilterable carboplatin in children. *Cancer Chemother. Pharmacol.* 42(3), 250–254 (1998).
 - 58 Guillet P, Monjanel S, Nicoara A *et al.* A Bayesian dosing method for carboplatin given by continuous infusion for 120 h. *Cancer Chemother. Pharmacol.* 40(2), 143–149 (1997).
 - 59 Jodrell DI, Reyno LM, Sridhara R *et al.* Suramin: development of a population pharmacokinetic model and its use with intermittent short infusions to control plasma drug concentration in patients with prostate cancer. *J. Clin. Oncol.* 12(1), 166–175 (1994).
 - 60 Eisenberger MA, Sinibaldi VJ, Reyno LM *et al.* Phase I and clinical evaluation of a pharmacologically guided regimen of suramin in patients with hormone-refractory prostate cancer. *J. Clin. Oncol.* 13(9), 2174–2186 (1995).
 - 61 Evans WE, Relling MV, Rodman JH, Crom WR, Boyett JM, Pui CH. Conventional compared with individualized chemotherapy for childhood acute lymphoblastic leukemia. *N. Engl. J. Med.* 338(8), 499–505 (1998).
 - 62 Schmiegelow K. Advances in individual prediction of methotrexate toxicity: a review. *Br. J. Haematol.* 146(5), 489–503 (2009).
 - 63 Dasgupta A, Hammett-Stabler CA, McCudden CR. Therapeutic drug monitoring of antineoplastic drugs. In: *Therapeutic Drug Monitoring Data: A Concise Guide*. Hammett-Stabler CA, Dasgupta A (Eds). AACC Press, DC, USA, 209–220 (2007).
 - 64 Odoul F, Le Guellec C, Lamagnere JP *et al.* Prediction of methotrexate elimination after high dose infusion in children with acute lymphoblastic leukaemia using a population pharmacokinetic approach. *Fundam. Clin. Pharmacol.* 13(5), 595–604 (1999).
 - 65 van Haandel L, Becker ML, Leeder JS, Williams TD, Stobaugh JF. A novel high-performance liquid chromatography/mass spectrometry method for improved selective and sensitive measurement of methotrexate polyglutamation status in human red blood cells. *Rapid Commun. Mass Spectrom.* 23(23), 3693–3702 (2009).
 - 66 McCune JS, Holmberg LA. Busulfan in hematopoietic stem cell transplant setting. *Expert Opin. Drug Metab. Toxicol.* 5(8), 957–969 (2009).
 - 67 Russell JA, Kangaroo SB. Therapeutic drug monitoring of busulfan in transplantation. *Curr. Pharm. Des.* 14(20), 1936–1949 (2008).
 - 68 McCune JS, Gibbs JP, Slattery JT. Plasma concentration monitoring of busulfan: does it improve clinical outcome? *Clin. Pharmacokinet.* 39(2), 155–165 (2000).
 - 69 Rauh M, Stachel D, Kuhlen M, Groschl M, Holter W, Rascher W. Quantification of busulfan in saliva and plasma in haematopoietic stem cell transplantation in children: validation of liquid chromatography tandem mass spectrometry method. *Clin. Pharmacokinet.* 45(3), 305–316 (2006).
 - 70 Bouligand J, Boland I, Valteau-Couanet D *et al.* In children and adolescents, the pharmacodynamics of high-dose busulfan is dependent on the second alkylating agent used in the combined regimen (melphalan or thiotepe). *Bone Marrow Transplant.* 32(10), 979–986 (2003).
 - 71 Vassal G, Gouyette A, Hartmann O, Pico JL, Lemerle J. Pharmacokinetics of high-dose busulfan in children. *Cancer Chemother. Pharmacol.* 24(6), 386–390 (1989).
 - 72 Schiltmeyer B, Klingebiel T, Schwab M *et al.* Population pharmacokinetics of oral busulfan in children. *Cancer Chemother. Pharmacol.* 52(3), 209–216 (2003).
 - 73 Soverini S, Martinelli G, Iacobucci I, Baccarani M. Imatinib mesylate for the treatment of chronic myeloid leukemia. *Expert Rev. Anticancer Ther.* 8(6), 853–864 (2008).
 - 74 Bullock JM, Smith PF, Booker BM *et al.* Development of a pharmacokinetic and bayesian optimal sampling model for individualization of oral busulfan in hematopoietic stem cell transplantation. *Ther. Drug Monit.* 28(1), 62–66 (2006).
 - 75 Tabak A, Hoffer E, Rowe JM, Krivoy N. Monitoring of busulfan area under the curve: estimation by a single measurement. *Ther. Drug Monit.* 23(5), 526–528 (2001).
 - 76 Vaughan WP, Carey D, Perry S, Westfall AO, Salzman DE. A limited sampling strategy for pharmacokinetic directed therapy with intravenous busulfan. *Biol. Blood Marrow Transplant.* 8(11), 619–624 (2002).
 - 77 Bleyzac N, Souillet G, Magron P *et al.* Improved clinical outcome of paediatric bone marrow recipients using a test dose and Bayesian pharmacokinetic individualization of busulfan dosage regimens. *Bone Marrow Transplant.* 28(8), 743–751 (2001).
 - 78 Bleyzac N. The use of pharmacokinetic models in paediatric onco-haematology: effects on clinical outcome through the examples of busulfan and cyclosporine. *Fundam. Clin. Pharmacol.* 22(6), 605–608 (2008).
 - 79 Brice K, Valerie B, Claire G *et al.* Risk-adjusted monitoring of veno-occlusive disease following bayesian individualization of busulfan dosage for bone marrow transplantation in paediatrics. *Pharmacoepidemiol. Drug Safety* 17(2), 135–143 (2008).
 - 80 Salamone SJ, Benfield CN, Courtney JB *et al.* A rapid nanoparticle immunoassay to quantitate busulfan in plasma. *Biol. Blood Marrow Transplant.* 15(S1), 154 (2009).
 - 81 Courtney JB, Harney R, Li Y *et al.* Determination of busulfan in human plasma using an ELISA format. *Ther. Drug Monit.* 31(4), 489–494 (2009).
 - 82 Hawwa AF, Millership JS, Collier PS *et al.* Pharmacogenomic studies of the anticancer and immunosuppressive thiopurines mercaptopurine and azathioprine. *Br. J. Clin. Pharmacol.* 66(4), 517–528 (2008).
 - 83 Lennard L. The clinical pharmacology of 6-mercaptopurine. *Eur. J. Clin. Pharmacol.* 43(4), 329–339 (1992).
 - 84 McLeod HL. Therapeutic drug monitoring opportunities in cancer therapy. *Pharmacol. Ther.* 74(1), 39–54 (1997).
 - 85 Lennard L. Therapeutic drug monitoring of cytotoxic drugs. *Br. J. Clin. Pharmacol.* 52(Suppl. 1), 75S–87S (2001).
 - 86 Endresen L, Lie SO, Storm-Mathisen I, Rugstad HE, Stokke O. Pharmacokinetics of oral 6-mercaptopurine: relationship between plasma levels and urine excretion of parent drug. *Ther. Drug Monit.* 12(3), 227–234 (1990).
 - 87 Kapoor A, Figlin RA. Targeted inhibition of mammalian target of rapamycin for the treatment of advanced renal cell carcinoma. *Cancer* 115(16), 3618–3630 (2009).
 - 88 MacDonald A, Scarola J, Burke JT, Zimmerman JJ. Clinical pharmacokinetics and therapeutic drug monitoring of sirolimus. *Clin. Ther.* 22(Suppl. B), B101–B121 (2000).
 - 89 Marty FM, Lowry CM, Cutler CS *et al.* Voriconazole and sirolimus coadministration after allogeneic hematopoietic stem cell transplantation. *Biol. Blood Marrow Transplant.* 12(5), 552–559 (2006).
 - 90 Campone M, Levy V, Bourbouloux E *et al.* Safety and pharmacokinetics of paclitaxel and the oral mtor inhibitor everolimus in advanced solid tumours. *Br. J. Cancer* 100(2), 315–321 (2009).
 - 91 Cattaneo D, Cortinovis M, Baldelli S, Gotti E, Remuzzi G, Perico N. Limited sampling strategies for the estimation of sirolimus daily exposure in kidney transplant recipients on a calcineurin inhibitor-free regimen. *J. Clin. Pharmacol.* 49(7), 773–781 (2009).

- 92 Sanchez-Fructuoso AI. Everolimus: an update on the mechanism of action, pharmacokinetics and recent clinical trials. *Expert Opin. Drug Metab. Toxicol.* 4(6), 807–819 (2008).
- 93 Ellard SL, Clemons M, Gelmon KA *et al.* Randomized Phase II study comparing two schedules of everolimus in patients with recurrent/metastatic breast cancer: NCIC clinical trials group ind.163. *J. Clin. Oncol.* 27(27), 4536–4541 (2009).
- 94 Hudes GR, Berkenblit A, Feingold J, Atkins MB, Rini BI, Dutcher J. Clinical trial experience with temsirolimus in patients with advanced renal cell carcinoma. *Semin. Oncol.* 36(Suppl. 3), S26–S36 (2009).
- 95 Sarkaria JN, Schwinger P, Schild SE *et al.* Phase I trial of sirolimus combined with radiation and cisplatin in non-small cell lung cancer. *J. Thorac. Oncol.* 2(8), 751–757 (2007).
- 96 Malizzia LJ, Hsu A. Temsirolimus, an mTOR inhibitor for treatment of patients with advanced renal cell carcinoma. *Clin. J. Oncol. Nurs.* 12(4), 639–646 (2008).
- 97 Joerger M, Schellens JH, Beijnen JH. Therapeutic drug monitoring of non-anticancer drugs in cancer patients. *Methods Find. Exp. Clin. Pharmacol.* 26(7), 531–545 (2004).
- 98 Saif MW, Choma A, Salamone SJ, Chu E. Pharmacokinetically guided dose adjustment of 5-fluorouracil: a rational approach to improving therapeutic outcomes. *J. Natl Cancer Inst.* 101(22), 1543–1552 (2009).
- 99 Wei X, McLeod HL, McMurrough J, Gonzalez FJ, Fernandez-Salguero P. Molecular basis of the human dihydropyrimidine dehydrogenase deficiency and 5-fluorouracil toxicity. *J. Clin. Invest.* 98(3), 610–615 (1996).
- 100 Gamelin E, Boisdron-Celle M, Guerin-Meyer V *et al.* Correlation between uracil and dihydrouracil plasma ratio, fluorouracil (5-FU) pharmacokinetic parameters, and tolerance in patients with advanced colorectal cancer: a potential interest for predicting 5-FU toxicity and determining optimal 5-FU dosage. *J. Clin. Oncol.* 17(4), 1105 (1999).
- 101 Milano G, Etienne MC, Cassuto-Viguier E *et al.* Influence of sex and age on fluorouracil clearance. *J. Clin. Oncol.* 10(7), 1171–1175 (1992).
- 102 Gamelin E, Delva R, Jacob J *et al.* Individual fluorouracil dose adjustment based on pharmacokinetic follow-up compared with conventional dosage: results of a multicenter randomized trial of patients with metastatic colorectal cancer. *J. Clin. Oncol.* 26(13), 2099–2105 (2008).
- Study demonstrating the efficacy of pharmacokinetic-guided dose adjustment (TDM) in 5-fluorouracil therapy.
- 103 Sawyers CL, Druker B. Tyrosine kinase inhibitors in chronic myeloid leukemia. *Cancer J. Sci. Am.* 5(2), 63–69 (1999).
- 104 Kumar L. Chronic myelogenous leukaemia (CML): an update. *Natl Med. J. India* 19(5), 255–263 (2006).
- 105 Gambacorti-Passerini CB, Gunby RH, Piazza R, Galierta A, Rostagno R, Scapozza L. Molecular mechanisms of resistance to imatinib in Philadelphia-chromosome-positive leukaemias. *Lancet Oncol.* 4(2), 75–85 (2003).
- 106 Singh N, Kumar L, Meena R, Velpandian T. Drug monitoring of imatinib levels in patients undergoing therapy for chronic myeloid leukaemia: comparing plasma levels of responders and non-responders. *Eur. J. Clin. Pharmacol.* 65(6), 545–549 (2009).
- Study demonstrating the pharmacokinetic variability between responders and nonresponders to imatinib, as well as the potential utility of TDM.
- 107 Larson RA, Druker BJ, Guilhot F *et al.* Imatinib pharmacokinetics and its correlation with response and safety in chronic-phase chronic myeloid leukemia: a subanalysis of the iris study. *Blood* 111(8), 4022–4028 (2008).
- 108 Jabbour E, Kantarjian H, Jones D *et al.* Frequency and clinical significance of BCR–ABL mutations in patients with chronic myeloid leukemia treated with imatinib mesylate. *Leukemia* 20(10), 1767–1773 (2006).
- 109 Branford S, Rudzki Z, Walsh S *et al.* Detection of BCR–ABL mutations in patients with CML treated with imatinib is virtually always accompanied by clinical resistance, and mutations in the ATP phosphate-binding loop (p-loop) are associated with a poor prognosis. *Blood* 102(1), 276–283 (2003).
- 110 Wilkinson GR. Cytochrome P4503A (CYP3A) metabolism: prediction of *in vivo* activity in humans. *J. Pharmacokinet. Biopharm.* 24(5), 475–490 (1996).
- 111 Burk O, Wojnowski L. Cytochrome P450 3A and their regulation. *Naunyn Schmiedebergs Arch. Pharmacol.* 369(1), 105–124 (2004).
- 112 Illmer T, Schaich M, Platzbecker U *et al.* P-glycoprotein-mediated drug efflux is a resistance mechanism of chronic myelogenous leukemia cells to treatment with imatinib mesylate. *Leukemia* 18(3), 401–408 (2004).
- 113 Druker BJ, Tamura S, Buchdunger E *et al.* Effects of a selective inhibitor of the abl tyrosine kinase on the growth of BCR–ABL positive cells. *Nat. Med.* 2(5), 561–566 (1996).
- 114 Peng B, Lloyd P, Schran H. Clinical pharmacokinetics of imatinib. *Clin. Pharmacokinet.* 44(9), 879–894 (2005).
- 115 Liegl-Atzwanger B, Fletcher JA, Fletcher CD. Gastrointestinal stromal tumors. *Virchows Arch.* 456(2), 111–127
- 116 Joensuu H. Gastrointestinal stromal tumor (GIST). *Ann. Oncol.* 17(Suppl. 10), X280–X286 (2006).
- 117 Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Arch. Pathol. Lab Med.* 130(10), 1466–1478 (2006).
- 118 Heinrich MC, Corless CL, Demetri GD *et al.* Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J. Clin. Oncol.* 21(23), 4342–4349 (2003).
- 119 Demetri GD, Wang Y, Wehrle E *et al.* Imatinib plasma levels are correlated with clinical benefit in patients with unresectable/metastatic gastrointestinal stromal tumors. *J. Clin. Oncol.* 27(19), 3141–3147 (2009).
- 120 Sciot R, Debicq-Rychter M. GIST under imatinib therapy. *Semin. Diagn. Pathol.* 23(2), 84–90 (2006).
- 121 Antonescu CR, Besmer P, Guo T *et al.* Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. *Clin. Cancer Res.* 11(11), 4182–4190 (2005).
- 122 Widmer N, Decosterd LA, Csajka C *et al.* Imatinib plasma levels: correlation with clinical benefit in GIST patients. *Br. J. Cancer* 102, 1198–1199 (2010).
- 123 Wang L, Giannoudis A, Lane S, Williamson P, Pirmohamed M, Clark RE. Expression of the uptake drug transporter hOCT1 is an important clinical determinant of the response to imatinib in chronic myeloid leukemia. *Clin. Pharmacol. Ther.* 83(2), 258–264 (2008).
- 124 Rochat B, Fayet A, Widmer N *et al.* Imatinib metabolite profiling in parallel to imatinib quantification in plasma of treated patients using liquid chromatography–mass spectrometry. *J. Mass Spectrom.* 43(6), 736–752 (2008).
- 125 Prenen H, Guetens G, De Boeck G, Highley M, van Oosterom AT, de Bruijn EA. Everolimus alters imatinib blood partition in favour of the erythrocyte. *J. Pharm. Pharmacol.* 58(8), 1063–1066 (2006).
- 126 Herbst RS. Review of epidermal growth factor receptor biology. *Int. J. Radiat. Oncol. Biol. Phys.* 59(2 Suppl.), 21–26 (2004).

- 127 Bergman E, Forsell P, Persson EM *et al.* Pharmacokinetics of gefitinib in humans: the influence of gastrointestinal factors. *Int. J. Pharm.* 341(1–2), 134–142 (2007).
- 128 Swaisland HC, Smith RP, Laight A *et al.* Single-dose clinical pharmacokinetic studies of gefitinib. *Clin. Pharmacokinet.* 44(11), 1165–1177 (2005).
- 129 Swaisland H, Laight A, Stafford L *et al.* Pharmacokinetics and tolerability of the orally active selective epidermal growth factor receptor tyrosine kinase inhibitor zoladix in healthy volunteers. *Clin. Pharmacokinet.* 40(4), 297–306 (2001).
- 130 Wilson CG, O'Mahony B, Connolly SM *et al.* Do gastrointestinal transit parameters influence the pharmacokinetics of gefitinib? *Int. J. Pharm.* 376(1–2), 7–12 (2009).
- 131 Moyer JD, Barbacci EG, Iwata KK *et al.* Induction of apoptosis and cell cycle arrest by cp-358,774, an inhibitor of epidermal growth factor receptor tyrosine kinase. *Cancer Res.* 57(21), 4838–4848 (1997).
- 132 Moore MJ, Goldstein D, Hamm J *et al.* Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a Phase III trial of the national cancer institute of Canada clinical trials group. *J. Clin. Oncol.* 25(15), 1960–1966 (2007).
- 133 Ling J, Johnson KA, Miao Z *et al.* Metabolism and excretion of erlotinib, a small molecule inhibitor of epidermal growth factor receptor tyrosine kinase, in healthy male volunteers. *Drug Metab. Dispos.* 34(3), 420–426 (2006).
- 134 Lu JF, Eppler SM, Wolf J *et al.* Clinical pharmacokinetics of erlotinib in patients with solid tumors and exposure-safety relationship in patients with non-small cell lung cancer. *Clin. Pharmacol. Ther.* 80(2), 136–145 (2006).
- 135 Thomas F, Rochaix P, White-Koning M *et al.* Population pharmacokinetics of erlotinib and its pharmacokinetic/pharmacodynamic relationships in head and neck squamous cell carcinoma. *Eur. J. Cancer* 45(13), 2316–2323 (2009).
- 136 Hanada K, Nishijima K, Ogata H, Atagi S, Kawahara M. Population pharmacokinetic analysis of cisplatin and its metabolites in cancer patients: possible misinterpretation of covariates for pharmacokinetic parameters calculated from the concentrations of unchanged cisplatin, ultrafiltered platinum and total platinum. *Jpn J. Clin. Oncol.* 31(5), 179–184 (2001).
- 137 Urien S, Brain E, Bugat R *et al.* Pharmacokinetics of platinum after oral or intravenous cisplatin: a Phase I study in 32 adult patients. *Cancer Chemother. Pharmacol.* 55(1), 55–60 (2005).
- 138 Salas S, Mercier C, Ciccolini J *et al.* Therapeutic drug monitoring for dose individualization of cisplatin in testicular cancer patients based upon total platinum measurement in plasma. *Ther. Drug Monit.* 28(4), 532–539 (2006).
- 139 Harland SJ, Gumbrell LA, Horwich A. Carboplatin dose in combination chemotherapy for testicular cancer. *Eur. J. Cancer* 27(6), 691–695 (1991).
- 140 Egorin MJ, Van Echo DA, Olman EA, Whitacre MY, Forrest A, Aisner J. Prospective validation of a pharmacologically based dosing scheme for the cis-diammine-dichloroplatinum(II) analogue diamminecyclobutanedicarboxylatoplatinum. *Cancer Res.* 45(12 Pt 1), 6502–6506 (1985).
- 141 Chatelut E, Pivot X, Otto J *et al.* A limited sampling strategy for determining carboplatin auc and monitoring drug dosage. *Eur. J. Cancer* 36(2), 264–269 (2000).
- 142 Veal GJ, Foot A, McDowell H, Ellershaw C, Pearson AD, Boddy AV. Optimization of high dose carboplatin treatment in children with stage IV soft tissue sarcoma (SIOP/UKCCSG MMT 98 study) by real-time pharmacokinetic monitoring. *Proc. Am. Assoc. Cancer Res.* 43, 1364 (2002).
- 143 Nguyen L, Chatelut E, Chevreau C *et al.* Population pharmacokinetics of total and unbound etoposide. *Cancer Chemother. Pharmacol.* 41(2), 125–132 (1998).
- 144 You B, Tranchand B, Girard P *et al.* Etoposide pharmacokinetics and survival in patients with small cell lung cancer: a multicentre study. *Lung Cancer* 62(2), 261–272 (2008).
- 145 Elis A, Lishner M, Walker S, Atias D, Korenberg A, Koren G. Doxorubicin in lymphoma: association between pharmacokinetic variability and clinical response. *Ther. Drug Monit.* 32(1), 50–52 (2010).
- 146 Chen D, Song SH, Wientjes MG *et al.* Nontoxic suramin as a chemosensitizer in patients: dosing nomogram development. *Pharm. Res.* 23(6), 1265–1274 (2006).
- 147 Villalona-Calero MA, Wientjes MG, Otterson GA *et al.* Phase I study of low-dose suramin as a chemosensitizer in patients with advanced non-small cell lung cancer. *Clin. Cancer Res.* 9(9), 3303–3311 (2003).
- 148 Kahan BD, Napoli KL, Kelly PA *et al.* Therapeutic drug monitoring of sirolimus: correlations with efficacy and toxicity. *Clin. Transplant.* 14(2), 97–109 (2000).

Appendix BIO01

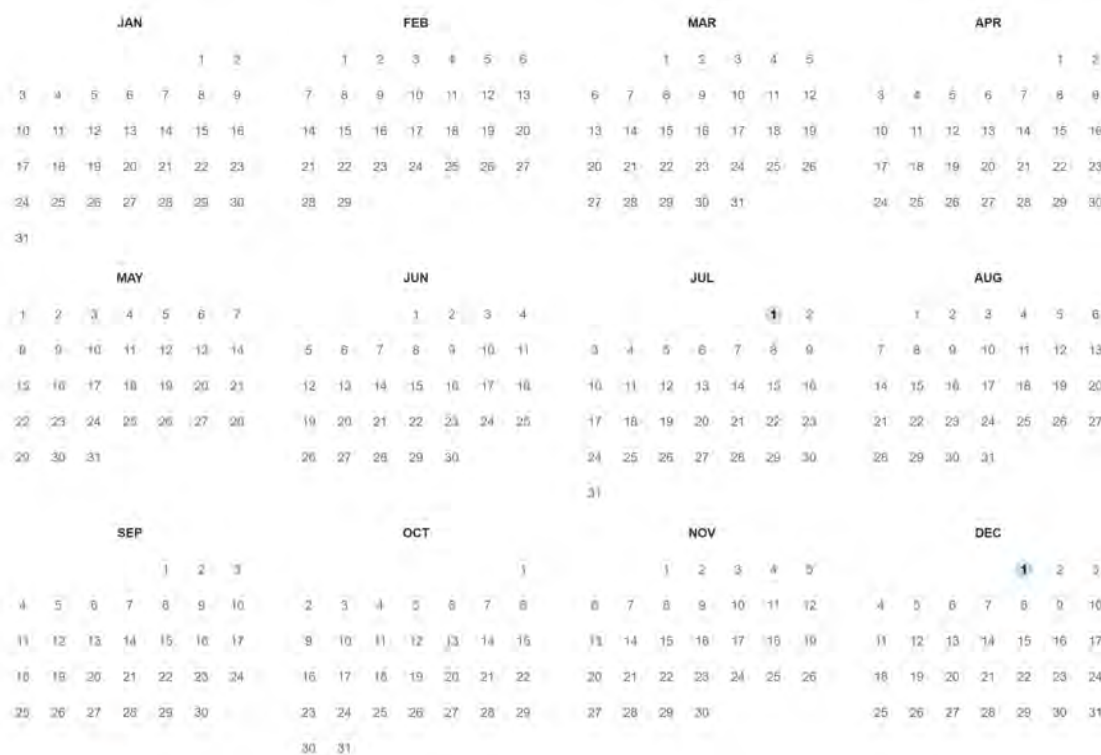


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Clinical Development Success Rates 2006-2015



June 2016

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Executive Summary

This is the largest study of clinical drug development success rates to date. Over the last decade, 2006-2015, a total of 9,985 clinical and regulatory phase transitions were recorded and analyzed from 7,455 development programs, across 1,103 companies in the Biomedtracker database. Phase transitions occur when a drug candidate advances into the next phase of development or is suspended by the sponsor. By calculating the number of programs progressing to the next phase vs. the total number progressing and suspended, we assessed the success rate at each of the four phases of development: Phase I, II, III, and regulatory filing. Having phase-by-phase data in hand, we then compared groups of diseases, drug modalities and other attributes to generate the most comprehensive analysis yet of biopharmaceutical R&D success.

This work was made possible due to the years of clinical program monitoring and data entry by Informa's Biomedtracker service. BIO has long partnered with Biomedtracker to calculate success rates based on this data. More recently, BIO and Biomedtracker partnered with Amplion, the inventors of BiomarkerBase, to analyze the effects of biomarkers in clinical trial success.

Key takeaways:

- The overall likelihood of approval (LOA) from Phase I for all developmental candidates was 9.6%, and 11.9% for all indications outside of Oncology.
- Rare disease programs and programs that utilized selection biomarkers had higher success rates at each phase of development vs. the overall dataset.
- Chronic diseases with high populations had lower LOA from Phase I vs. the overall dataset.
- Of the 14 major disease areas, Hematology had the highest LOA from Phase I (26.1%) and Oncology had the lowest (5.1%).
- Sub-indication analysis within Oncology revealed hematological cancers had 2x higher LOA from Phase I than solid tumors.
- Oncology drugs had a 2x higher rate of first cycle approval than Psychiatric drugs, which had the lowest percent of first-cycle review approvals. Oncology drugs were also approved the fastest of all 14 disease areas.
- Phase II clinical programs continue to experience the lowest success rate of the four development phases, with only 30.7% of developmental candidates advancing to Phase III.



Disease areas covered in this report:

- Allergy
- Autoimmune
- Cardiovascular
- Chronic High Prevalence Diseases
- Endocrine
- Gastroenterology
- Hematology
- Infectious Disease
- Metabolic
- Neurology
- Oncology
- Ophthalmology
- Psychiatry
- Rare Diseases
- Respiratory
- Urology

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Introduction

This study aimed to measure clinical development success rates to strengthen benchmarking metrics for drug development. To measure success rates for investigational drugs, we analyzed individual drug program phase transitions from January 1, 2006 to December 31, 2015. For the ten years studied, 9,985 transitions in the Biomedtracker database were analyzed. A phase transition is the movement out of a clinical phase – for example, advancing from Phase I to Phase II development, or being suspended after completion of Phase I development.

These transitions occurred in 7,455 clinical drug development programs, across 1,103 companies (both large and small), making this the largest study of its kind. With this broad set of data, we aimed to capture the diversity in drug development across levels of novelty, molecular modalities, and disease indications.

Only company-sponsored, FDA registration-enabling development programs were considered; investigator-sponsored studies were excluded from this analysis. A more detailed description of the data collection, composition, and analysis methodology are described at the end of this report under “Methods.”

Individual Phase transition success rates were determined by dividing the number that advanced to the next phase by the total number advanced and suspended. This “advanced and suspended” number is often referred to as “n” in this report, and should be taken into account when drawing conclusions from the success rate results.

One of the key measures of success used in this report is the Likelihood of Approval (LOA) from Phase I. This LOA success rate is simply a multiplication of all four Phases success rates, a compounded probability calculation. For example, if each phase had a 50% chance of success, then the LOA from Phase I would be $0.5 \times 0.5 \times 0.5 \times 0.5 = 6.25\%$.

Phase Transition Success and Likelihood of Approval (LOA) - Overall

Consistent with previous studies of drug development phase transition success rates, we found Phase II success rates to be far lower than any other phase.¹ Phase I and III rates were substantially higher than Phase II, with Phase I slightly higher than Phase III. The highest success rate of the four development phases was the NDA/BLA filing phase.

The Phase I transition success rate was 63.2% (n=3,582). As this Phase is typically conducted for safety testing and is not dependent on efficacy results for candidates to advance, it is common for this phase to have the highest success rate among the clinical phases across most categories analyzed in this report. Phase I success rates may also benefit from delayed reporting bias, as some larger companies may not deem failed Phase I programs as material and thereby not report them in the public domain. The Phase II transition success rate (30.7%, n=3,862) was substantially lower than Phase I, and the lowest of the four phases studied. As this is generally the first stage where proof-of-concept is deliberately tested in human subjects, Phase II consistently had the lowest success rate of all phases. This is also the point in development where industry must decide whether to pursue the large, expensive Phase III studies and may decide to terminate development for multiple reasons including commercial viability. The second-lowest phase transition success rate was found in Phase III (58.1%, n=1,491). This is significant as most company-sponsored Phase III trials are the longest and most expensive trials to conduct.

The probability of FDA approval after submitting a New Drug Application (NDA) or Biologic License Application (BLA), taking into account re-submissions, was 85.3% (n=1,050). Multiplying these individual phase components to obtain the compound probability of progressing from Phase I to U.S. FDA approval (LOA) reveals that only 9.6% (n=9,985) of drug development programs successfully make it to market (**Figure 1**).

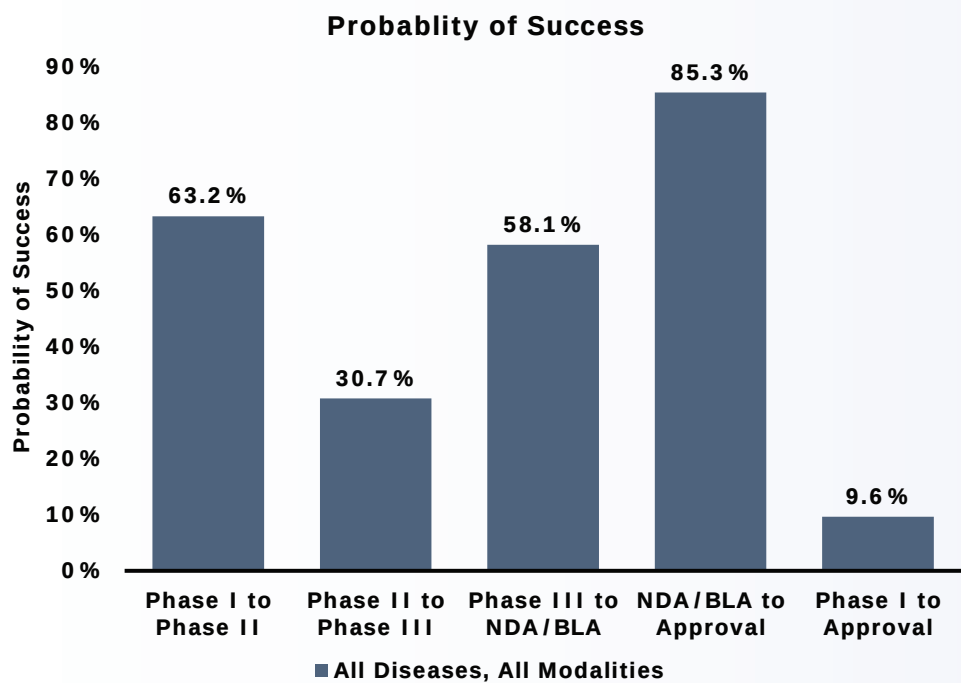


Figure 1. Phase transition success rates and LOA from Phase I for all diseases, all modalities.

Phase Transition Success and Likelihood of Approval (LOA) - by Disease

We segmented major disease areas according to the convention used by Biomedtracker, and categorized 21 major diseases and 558 indications for the 2006-2015 timeframe. For reporting at the disease area level, we analyzed only major diseases with more than 100 total transitions from Phase I to NDA/BLA approval. This resulted in 14 categorized disease areas: Allergy, Autoimmune, Cardiovascular, Endocrine, Hematology, Infectious disease, Gastroenterology (non-IBD), Metabolic, Neurology, Oncology, Ophthalmology, Psychiatry, Respiratory, and Urology. Disease areas with n < 100 were placed into the “Other” category. This includes Dermatology, Renal, Obstetrics, Rheumatology (for non-autoimmune indications), Dental, and Orthopedics.

As can be seen in **Figures 2a**, there is a wide range of Likelihood of Approval (LOA) from Phase I. At the high end, Hematology towers over the other groups at 26.1% (n=283). A large portion of Hematology transitions came from Hemophilia, Anemia, and Blood Protein Deficiencies, Thrombocytopenia, and Hemostasis. Some of these Hemophilia indications had overall LOA that reached above 50%. This more than offset some of the weaker Hematology success rates that were observed in Venous Thromboembolism and Neutropenia. Hematology’s LOA from Phase I was 5x the success rate for Oncology, which at 5.1% (n=3,163) had the lowest of all the major disease areas.

The next-highest LOA from Phase I under Hematology’s 26.1% was Infectious Disease with an impressive 19.1% (n=916). Five disease areas follow closely in the 14-17% range: Ophthalmology > Other > Metabolic > Gastroenterology > Allergy. Below 14% there is a third group of diseases that was slightly above the overall average of 9.6%: Endocrine > Respiratory > Urology > Autoimmune. Falling under the overall LOA of 9.6% was a fourth group made up of four disease areas: Neurology > Cardiovascular > Psychiatry > Oncology. The fact that Oncology and Neurology had the two highest n values while also having low LOA values suggests that these two disease categories are a significant factor in bringing down the overall industry LOA.

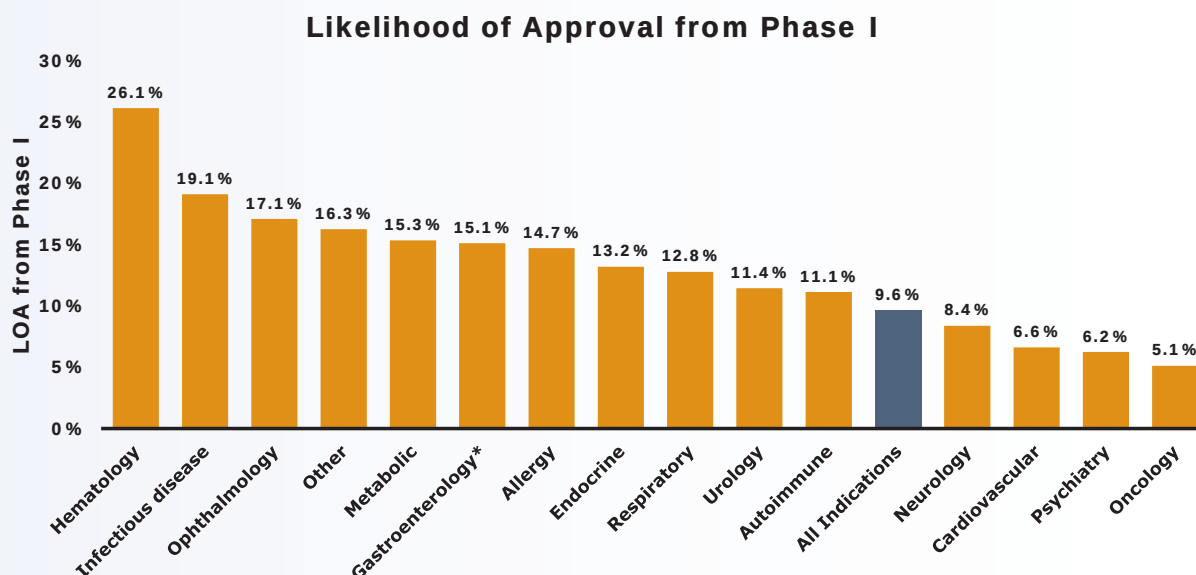


Figure 2a. Chart of LOA from Phase I, displayed highest to lowest by disease area.

Phase Success	Phase I to Phase II		Phase II to Phase III		Phase III to NDA/BLA		NDA/BLA to Approval	
	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success
Hematology	86	73.3%	83	56.6%	64	75.0%	50	84.0%
Infectious disease	347	69.5%	286	42.7%	150	72.7%	133	88.7%
Ophthalmology	66	84.8%	101	44.6%	60	58.3%	40	77.5%
Other	96	66.7%	116	39.7%	46	69.6%	43	88.4%
Metabolic	95	61.1%	84	45.2%	35	71.4%	27	77.8%
Gastroenterology*	41	75.6%	56	35.7%	33	60.6%	26	92.3%
Allergy	37	67.6%	40	32.5%	14	71.4%	16	93.8%
Endocrine	299	58.9%	242	40.1%	143	65.0%	107	86.0%
Respiratory	150	65.3%	196	29.1%	45	71.1%	37	94.6%
Urology	21	57.1%	52	32.7%	21	71.4%	14	85.7%
Autoimmune	297	65.7%	319	31.7%	135	62.2%	86	86.0%
All Indications	3582	63.2%	3862	30.7%	1491	58.1%	1050	85.3%
Neurology	462	59.1%	465	29.7%	216	57.4%	161	83.2%
Cardiovascular	209	58.9%	237	24.1%	110	55.5%	76	84.2%
Psychiatry	154	53.9%	169	23.7%	70	55.7%	58	87.9%
Oncology	1222	62.8%	1416	24.6%	349	40.1%	176	82.4%
Likelihood of Approval	Phase I to Approval		Phase II to Approval		Phase III to Approval		NDA/BLA to Approval	
	LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA
Hematology	283	26.1%	197	35.7%	114	63.0%	50	84.0%
Infectious disease	916	19.1%	569	27.5%	283	64.5%	133	88.7%
Ophthalmology	267	17.1%	201	20.1%	100	45.2%	40	77.5%
Other	301	16.3%	205	24.4%	89	61.5%	43	88.4%
Metabolic	241	15.3%	146	25.1%	62	55.6%	27	77.8%
Gastroenterology*	156	15.1%	115	20.0%	59	55.9%	26	92.3%
Allergy	107	14.7%	70	21.8%	30	67.0%	16	93.8%
Endocrine	791	13.2%	492	22.4%	250	55.9%	107	86.0%
Respiratory	428	12.8%	278	19.6%	82	67.3%	37	94.6%
Urology	108	11.4%	87	20.0%	35	61.2%	14	85.7%
Autoimmune	837	11.1%	540	17.0%	221	53.5%	86	86.0%
All Indications	9985	9.6%	6403	15.3%	2541	49.6%	1050	85.3%
Neurology	1304	8.4%	842	14.2%	377	47.8%	161	83.2%
Cardiovascular	632	6.6%	423	11.2%	186	46.7%	76	84.2%
Psychiatry	451	6.2%	297	11.6%	128	49.0%	58	87.9%
Oncology	3163	5.1%	1941	8.1%	525	33.0%	176	82.4%

Figure 2b. Phase transition success and LOA by disease. Table of phase transition success and LOA by disease with corresponding n values. 'Advanced or Suspended' refers to the total number of transitions used to calculate each success rate, with the n value noted in the text. The LOA n value is the total 'Advanced or Suspended' transitions of all phases used to calculate LOA. 'Phase Success' is the probability of successfully advancing to the next phase, whereas 'Phase LOA' is the probability of FDA approval for drugs from this phase of development. *Gastroenterology does not include IBD.

Phase I Transition Success Rates by Disease

Success rates for Phase I ranged from 53.9% to 84.8%, with the average for all disease indications coming in at 63.2%. Looking at the distribution, we find that most disease area Phase I success rates cluster within +/-10% of the overall Phase I success rate. Two disease areas were outliers, and they are both to the upside. Ophthalmology registered an 84.8% (n=66) success rate, which was substantially higher (by >20%) than the overall Phase I success rate. Gastroenterology programs also exhibited an above average rate of successfully overcoming initial clinical safety hurdles with a 75.6% (n=41) Phase I success rate.

Phase II Transition Success Rates by Disease

In every disease area, Phase II had the lowest transition success rate of the four phases. As shown in **Figure 3**, Phase II success rates ranged from a high of 56.6% (Hematology, n=83) to a low of 23.7% (Psychiatry, n=169). Although it is widely known that drug program attrition is high in Phase II, it is interesting to find that the rate of success can vary by 33% among disease groups. The only Phase II success rate above 50% was seen in Hematology, which largely explains how that indication attained the highest LOA from Phase I.

Excluding Hematology, we can group the Phase II success rates into three clusters: success rates below the 30% overall success rate, those 31-36%, and those in the 40-45% range. Unlike what is observed in the LOA from Phase I, Oncology does not have the lowest success rate for Phase II. Cardiovascular and Psychiatry both registered slightly below the 25% success rate seen for Oncology.

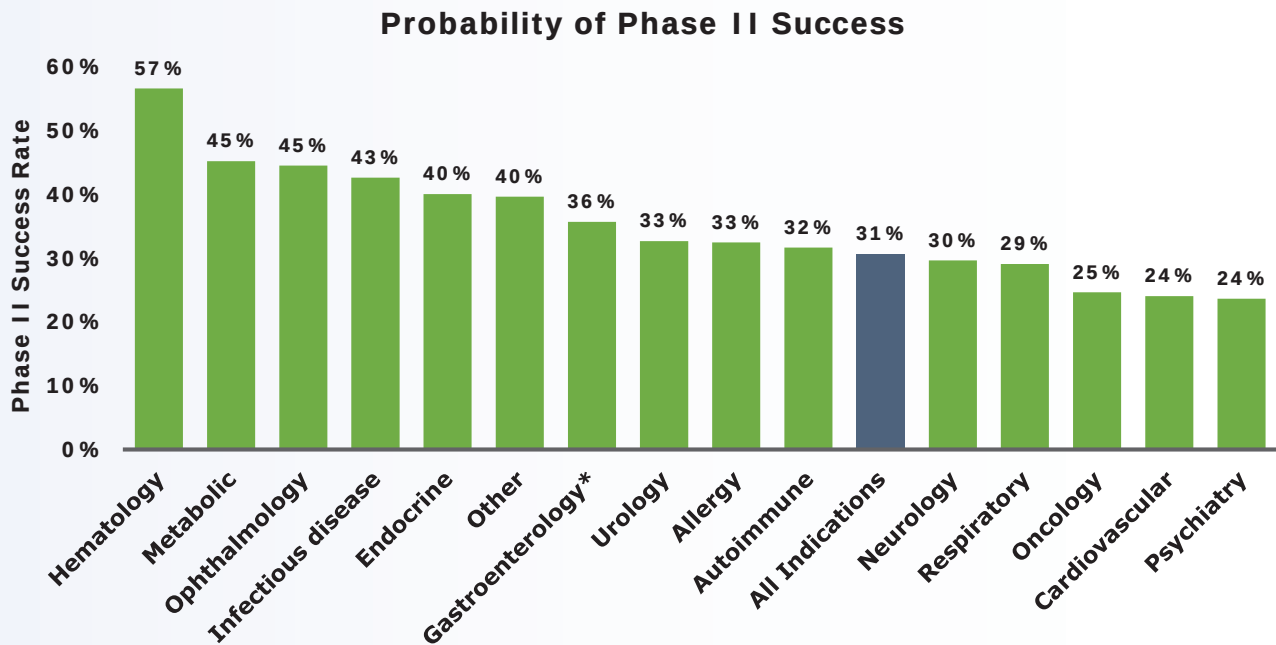


Figure 3. Phase II transition success rates by disease area. Categories are listed from highest to lowest based on the probability of transitioning from Phase II to Phase III. *Gastroenterology does not include IBD.

Phase III Transition Success Rates by Disease

For Phase III transition success rates, Oncology was the outlier with the lowest transition success rate. As seen in **Figure 4**, the Phase III success rates for 14 specific disease areas clustered into two ranges: near 70% and 55-65%. This places Oncology into a group of its own at just 40.1% (n=349).

In addition to Oncology, Neurology, Psychiatry and Cardiovascular were also below the overall Phase III success rate of 58.1% (n=1,491) at 57.4%, 55.7%, and 55.5%, respectively. Each of these areas included disease indications with large patient populations. Later in this report, we break down these high prevalence diseases and compare them with low prevalence disease areas.

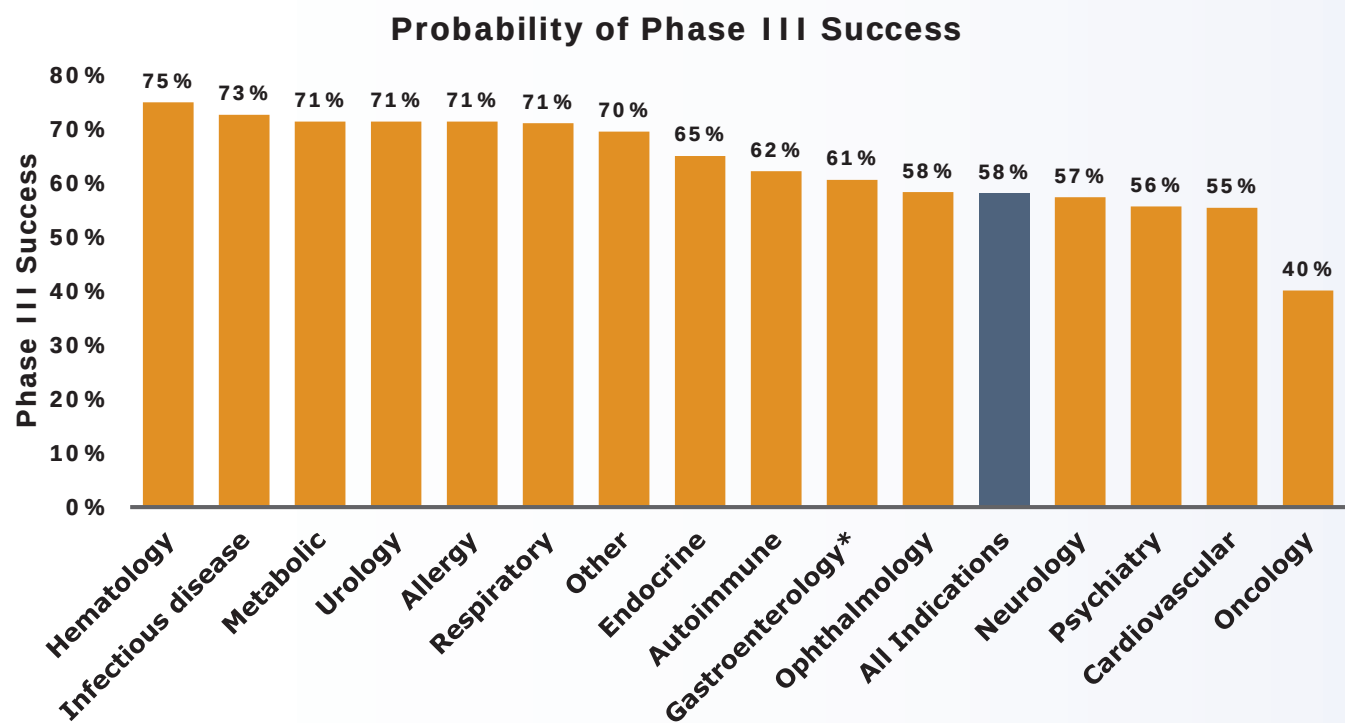


Figure 4. Phase III transition success rates by disease area. Categories are listed from highest to lowest based on the probability of transitioning from Phase II to NDA/BLA filing. *Gastroenterology does not include IBD.

NDA/BLA Submission Success Rates

NDA/BLA transition success rates (approval rates) for the disease areas listed in **Figure 2b** ranged from the low end of 77.5% (Ophthalmology) to a high of 94.6% (Respiratory). The distribution of rates (17.1%) were within the tightest range among the four phases analyzed in this report. These rates are the result of eventual success, not success on first review, meaning some programs may have as many as four Complete Response Letters (CRLs) and attempts at approval. This unrestricted time-frame and number of re-submissions pushes the overall success above 85% across all diseases.

When looking at how many original NDA/BLA filings were approved on the first review by FDA, the rates are far from concentrated (**Figure 5**). In fact, Psychiatry had only a 37% chance of first-cycle approval vs. Oncology at nearly 80%. Although this is an extreme range, upon subsequent submissions and reviews, both of these disease areas ended up with 91% of original drug indication applications being approved. There was a large increase in cumulative success rates after the second submission, but only marginal increases after the third review.

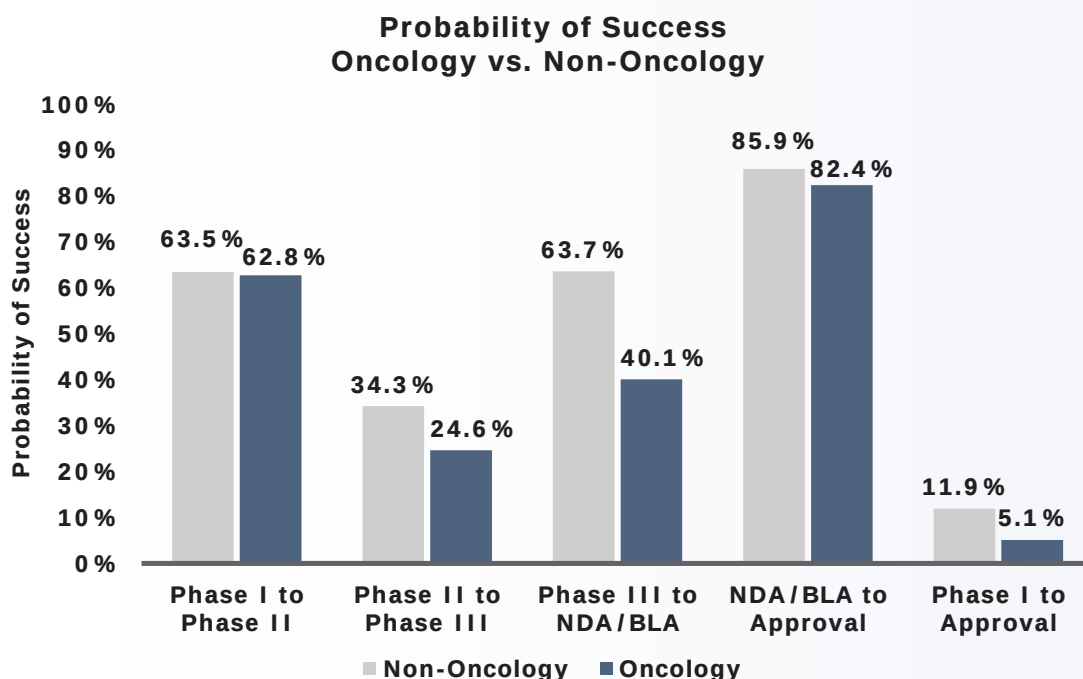
Time from filing to approval also varied by disease area. Neurology drugs took the longest to approve on average, at 2 years, while Oncology drugs were approved almost twice as fast at 1.1 years. Many Oncology drugs for unmet medical need may have benefited from expedited approval pathways and associated increased interactions with FDA such as Breakthrough Therapy and Accelerated Approval, contributing to the faster overall time to approval. As might be expected, calculating time to approval for all disease areas put the time to approval in the middle of these extremes, at 1.6 years.

Disease Area	% Approved on 1st Review	% Approved by 2nd Review	% Ultimately Approved	Filing to Approval Time (Years)
Oncology	79%	89%	89%	1.1
Allergy	71%	93%	93%	1.3
Respiratory	71%	94%	94%	1.6
Cardiovascular	69%	83%	85%	1.4
Infectious disease	69%	86%	92%	1.4
Urology	64%	73%	82%	1.7
Autoimmune	63%	82%	86%	1.6
Metabolic	63%	83%	83%	1.5
Ophthalmology	62%	69%	73%	1.3
All Diseases	61%	80%	86%	1.6
Hematology	60%	76%	90%	1.6
Gastroenterology	56%	84%	92%	1.8
Endocrine	56%	77%	83%	1.8
Neurology	45%	70%	81%	2.0
Psychiatry	37%	70%	91%	1.6

Figure 5. Time to FDA approval and percent approved by FDA for original NDA/BLA filings only. Data shown does not include supplemental applications.

Oncology and Non-Oncology Diseases

Oncology drug development program transitions in the 2006-2015 period accounted for 31% of the 9,985 total transitions. With the lowest LOA from Phase I (5.1%, n=3,163), Oncology had an outsized effect on the overall industry success rate. To further understand this contribution, we compared phase transition success rates and LOA for non-oncology development programs against oncology development programs alone. **Figure 6** shows Phase success rates and LOA from Phase I for oncology and non-oncology development programs. The LOA from Phase I across non-oncology indications was twice that for oncology alone, at 11.9% (n=6,822). Looking at individual phase transition success rates, it is clear that Phase III transition success rates were the reason Oncology ended up with the lowest overall success across our 14 disease categories. Oncology Phase III success was 23% lower than Non-Oncology disease areas.



Phase Success		Phase I to Phase II		Phase II to Phase III		Phase III to NDA/BLA		NDA/BLA to Approval	
		Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success
Oncology		1222	62.8%	1416	24.6%	349	40.1%	176	82.4%
Non-Oncology		2360	63.5%	2446	34.3%	1142	63.7%	874	85.9%
Likelihood of Approval		Phase I to Approval		Phase II to Approval		Phase III to Approval		NDA/BLA to Approval	
		LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA
Oncology		3163	5.1%	1941	8.1%	525	33.0%	176	82.4%
Non-Oncology		6822	11.9%	4462	18.7%	2016	54.7%	874	85.9%

Figure 6. Oncology vs. Non-Oncology phase transition success rates and LOA. Top: Chart of LOA from Phase I. Bottom: Table of phase transition success rates and LOA for Oncology vs. Non-Oncology indications, with corresponding n values. 'Advanced or Suspended' refers to the total number of transitions used to calculate each success rate, with the n value noted in the text. The LOA n value is the total 'Advanced or Suspended' transitions of all phases used to calculate LOA. 'Phase Success' is the probability of successfully advancing to the next phase, whereas 'Phase LOA' is the probability of FDA approval for drugs in this phase of development.

Oncology Sub-Indication Phase Transition Success Rates and LOA

Oncology drugs were further categorized into two main types of cancer: solid tumors and hematological cancers. Solid tumors had twice as many transitions in the data set (2,283 vs. 805), but only half the LOA from Phase I vs. hematological cancers (4.0% vs. 8.1%). These are shown in **Figure 7** in more detail.

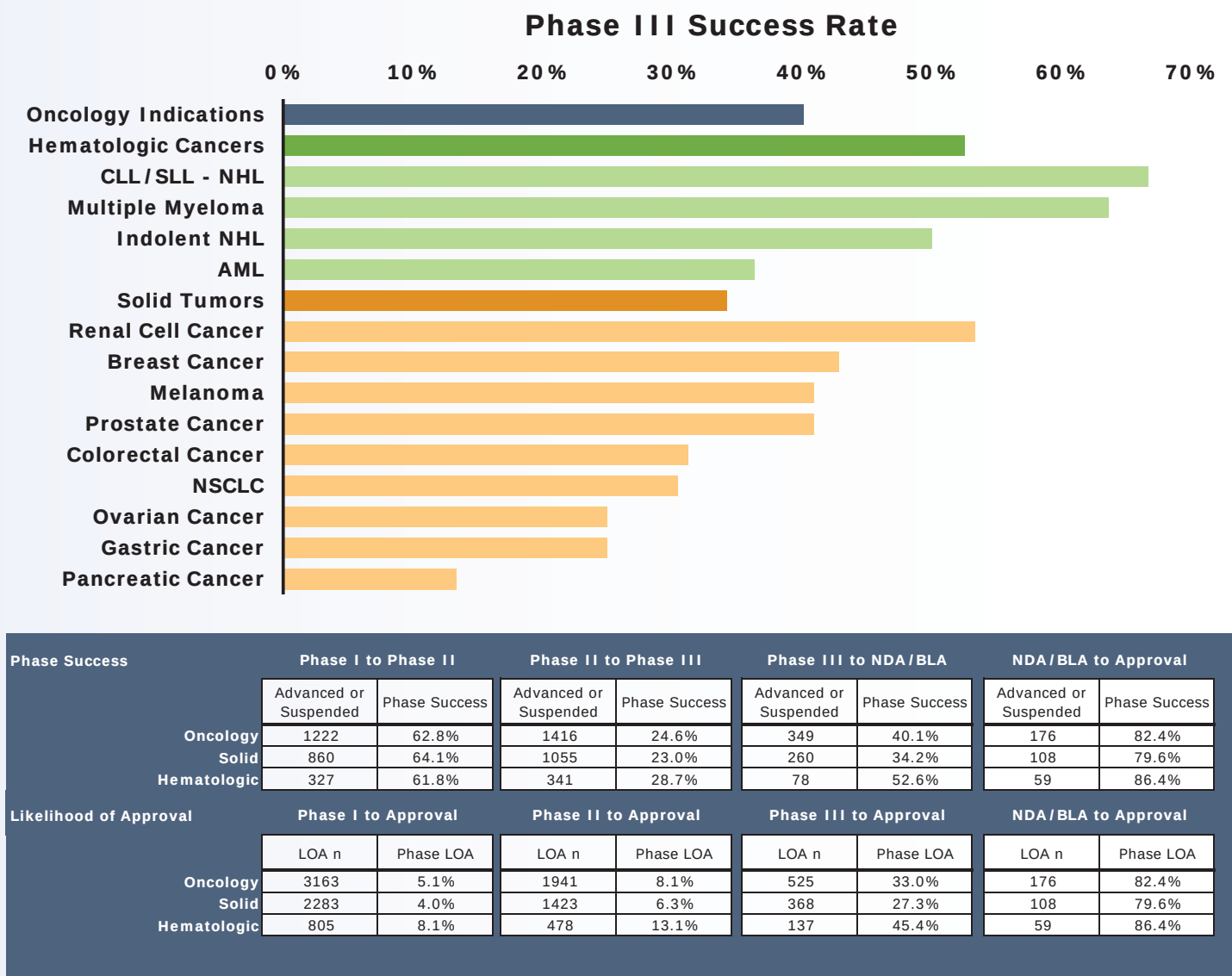


Figure 7. Phase transition success rates and LOA for Oncology indications with corresponding n values. ‘Advanced or Suspended’ refers to the total number of transitions used to calculate each success rate, with the n value noted in the text. The LOA n value is the total ‘Advanced or Suspended’ transitions of all phases used to calculate LOA. ‘Phase Success’ is the probability of successfully advancing to the next phase, whereas ‘Phase LOA’ is the probability of FDA approval for drugs in this phase of development.

Phase II transition success rates by sub-indication tended to range close to the overall 25% Oncology calculation for Phase II, +/-10%.

Narrowing in on Phase III transition success rates, only 34.2% of the 260 drug programs in solid tumor cancers were deemed sufficiently successful to file an NDA/BLA with the FDA. This was the underlying cause for the 2x difference we see in overall LOA, as the hematological cancer programs recorded a 52.6% success rate in Phase III. Since Phase III was identified as the weakest phase for Oncology, Phase III transition success rates for a number of major oncology sub-indications were included in **Figure 7**.

The solid tumor Phase III transition success rate (34.2%, n=260) ended up as the lowest for any of the major disease categories studied. Solid tumor drugs for pancreatic cancer seemed to have the toughest challenges in Phase III studies (13.3%, n=15). However, Phase III success rates for Ovarian and Gastric cancers also fell below 30%.

Hematological cancer Phase III transition success rates benefited from transition successes in CLL/SLL (66.7%, n=12) and MM (63.7%, n=11). ALL, Hodgkin's and CML had Phase III success rates of 100% but only had fewer than five completed clinical development programs each (data not shown). Only AML (36.4%, n=11) came in below 40% for Phase III, which helped the overall hematologic cancer Phase III success rate remain above 50%.

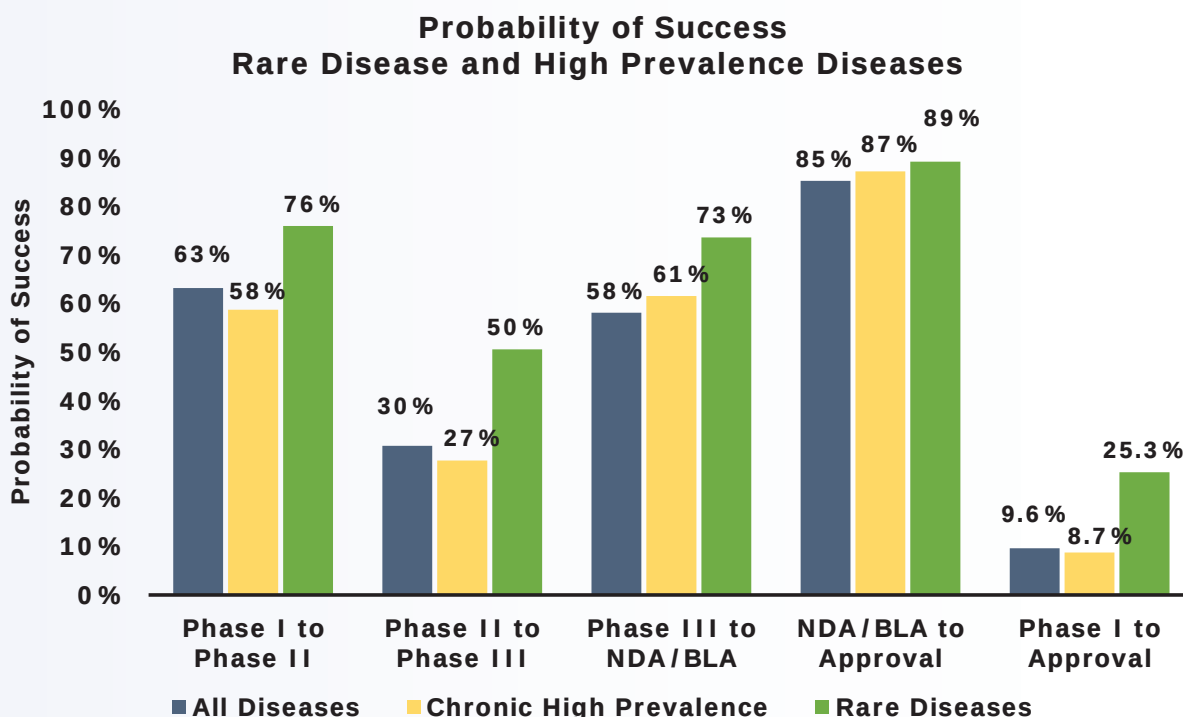
The NDA/BLA to approval success rate for all hematological cancers (86.4%, n=59) was impacted positively by Multiple Myeloma, ALL, and CML success, as each had more than five completed filings and 100% approval rates. The NDA/BLA success rate for all solid tumors was lower at 79.6% (n=108).

Abbreviated cancer indications:

- ALL - Acute Lymphocytic Leukemia
- AML - Acute Myelogenous Leukemia
- CLL - Chronic Lymphocytic Leukemia
- CML - Chronic myelogenous Leukemia
- MM - Multiple Myeloma
- NHL - Non-Hodgkin's Lymphoma
- NSCLC - Non-Small Cell Lung Cancer
- SLL - Small Lymphocytic Lymphoma

Rare Diseases and Chronic High Prevalence Diseases

In recent years, there has been an increase in funding for companies focused on rare diseases.² This is welcome news as there are reportedly 7,000 rare diseases and most do not have an approved therapeutic treatment.⁴ One question that is often asked is if the probabilities of success are any better for rare diseases, especially for those in which a particular defective gene has been confirmed as the sole contributor. On the other extreme, we have observed less venture funding for high prevalence, chronic diseases.² The question we wanted to explore is whether investors may have scaled back funding because there is a higher hurdle to developing and gaining approval for medicines that treat highly prevalent conditions.



Phase Success		Phase I to Phase II		Phase II to Phase III		Phase III to NDA/BLA		NDA/BLA to Approval	
		Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success
All Diseases		3582	63.2%	3862	30.7%	1491	58.1%	1050	85.3%
Chronic High Prevalence		732	58.7%	726	27.7%	268	61.6%	196	87.2%
Rare Diseases		150	76.0%	168	50.6%	110	73.6%	93	89.2%

Likelihood of Approval		Phase I to Approval		Phase II to Approval		Phase III to Approval		NDA/BLA to Approval	
		LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA
All Diseases		9985	9.6%	6403	15.3%	2541	49.6%	1050	85.3%
Chronic High Prevalence		1922	8.7%	1190	14.9%	464	53.7%	196	87.2%
Rare Diseases		521	25.3%	371	33.3%	203	65.7%	93	89.2%

Figure 8. Non-Oncology Rare disease and high prevalence, chronic disease. Top: Chart of phase transition success rates and LOA from Phase I, for rare and chronic, high prevalence. Bottom: Table of phase transition success and LOA by disease with corresponding n values. 'Advanced or Suspended' refers to the total number of transitions used to calculate each success rate, with the n value noted in the text. The LOA n value is the total 'Advanced or Suspended' transitions of all phases used to calculate LOA. 'Phase Success' is the probability of successfully advancing to the next phase, whereas 'Phase LOA' is the probability of FDA approval for drugs in this phase of development.

We isolated rare disease programs in the Biomedtracker database by first identifying all prior FDA Orphan-designated indications, then pooling all drug programs in these indications, regardless of whether they obtained FDA's Orphan designation. All Oncology indications were removed to make this rare disease analysis more concentrated on inborn genetic disorders. For chronic diseases, we first obtained a list of conditions from the Center for Medicare & Medicaid Services (CMS) Chronic Conditions Data Warehouse (CCW). We removed any cancer indications, then identified those disease with > 1 million patients afflicted with the disease in the United States.

With programs from both groups identified, we compared phase transition success rates and LOA as shown in **Figure 8**. At 25.3%, the overall LOA from Phase I for Non-Oncology rare diseases was 2.6x higher than the LOA for all diseases and 3x higher than the 8.7% LOA for chronic, high prevalence diseases. Chronic, high prevalence diseases accounted for almost 20% of the transitions, and Oncology, 31% of the transitions. The combined weighting of 50% of the dataset for these two categories with low LOAs (Chronic, high prevalence disease, 8.7% and Oncology, 5.7%) contributed significantly to the low overall industry LOA of 9.6%.

All four transition success rates were higher for the rare disease group than the overall dataset. The largest difference between was found in Phase II transition success rates (50.6% for rare disease vs 30.7% overall). Phase III and Phase I each had higher transition success rates by at least 10%.

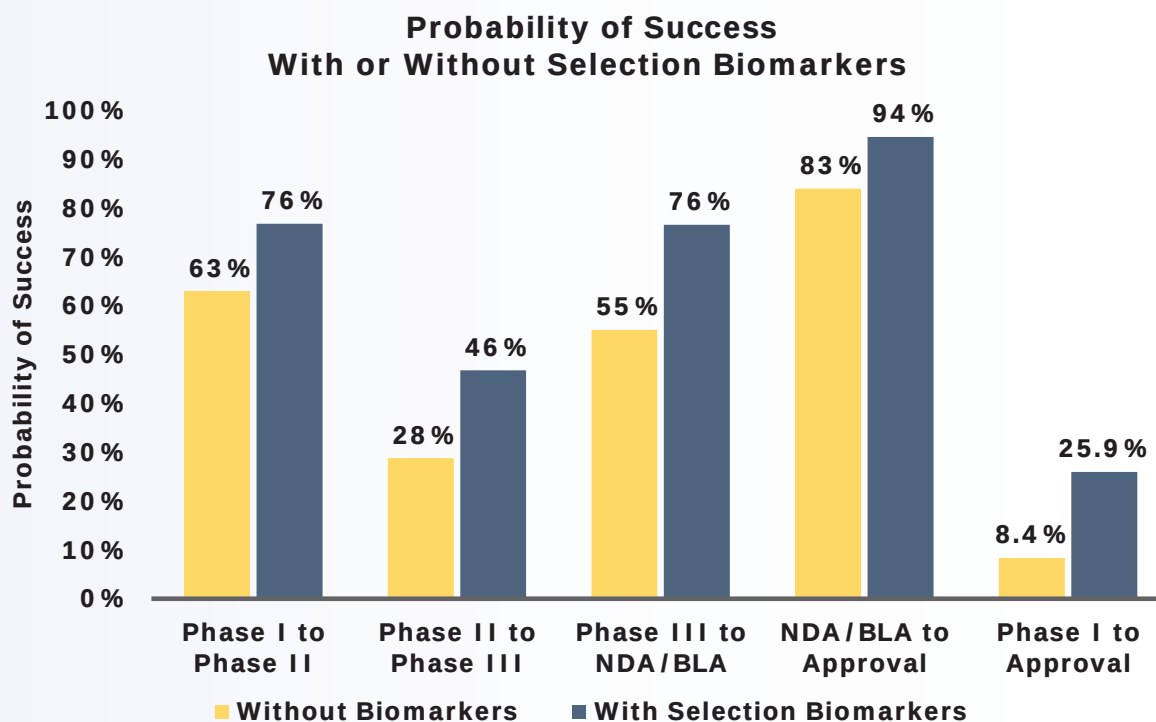
Chronic, high prevalence diseases transition success rates were lower in Phase I (58.7% vs 63.2%) and Phase II (27.7% vs. 30.7%) vs. the overall dataset. The opposite was seen in Phase III and NDA/BLA, where slightly higher rates were observed: 61.6% vs. 58.1% for Phase III and 87.2% vs. 85.3% for NDA/BLA.

As the chronic, high prevalence group in this study does not include Oncology, we compared these results with the Non-Oncology rates found in **Figure 6**. Although the chronic, high prevalence Phase III transition success rate is higher than that seen with all diseases, it is lower than the Non-Oncology transition success rates (61.6% vs. 63.7%). Furthermore, the LOA of 11.9% (n=6,822) for all Non-Oncology indications is 3% higher than for chronic, high prevalence diseases (8.7%), suggesting that these chronic indications are negatively impacting overall success rates outside Oncology.

Patient Selection Biomarker Programs

The use of biomarkers as inclusion or exclusion criteria, or 'selection biomarkers', for enrolling patients into clinical studies has increased dramatically since the sequencing of the human genome. We identified 512 phase transitions out of 9,985 (5%) that incorporated a selection biomarker for patient stratification. This was accomplished by mapping the NCT numbers (clinicaltrial.gov identifier) from Amplion's BiomarkerBase to programs in the Biomedtracker transition database.⁶ For programs that filed an NDA/BLA, we only included filings that used selection biomarkers in the Phase III study design.

The LOA from Phase I can be found in **Figure 9**. The benefit from selection biomarker use raises the LOA from Phase I to one in four compared to less than one in 10 when no selection biomarker was used.



Phase Success		Phase I to Phase II		Phase II to Phase III		Phase III to NDA/BLA		NDA/BLA to Approval	
		Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success
No Biomarkers		3480	63.0%	3396	28.8%	1254	55.0%	882	83.9%
Selection Biomarkers		43	76.7%	246	46.7%	132	76.5%	91	94.5%
Likelihood of Approval		Phase I to Approval		Phase II to Approval		Phase III to Approval		NDA/BLA to Approval	
		LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA
No Biomarkers		9012	8.4%	5532	13.3%	2136	46.2%	882	83.9%
Selection Biomarkers		512	25.9%	469	33.8%	223	72.3%	91	94.5%

Figure 9. Selection Biomarker phase transition success rates and LOA. Top: Chart of individual phase transition success rates and LOA from Phase I for all indications without and with selection biomarkers. Bottom: Table of Phase transition success and LOA by disease with corresponding n values. 'Advanced or Suspended' refers to the total number of transitions used to calculate each success rate, with the n value noted in the text. The LOA n value is the total 'Advanced or Suspended' transitions of all phases used to calculate LOA. 'Phase Success' is the probability of successfully advancing to the next phase, whereas 'Phase LOA' is the probability of FDA approval for drugs in this phase of development.

As shown in the table of **Figure 9**, a three-fold higher LOA from Phase 1 was calculated for programs that utilized selection biomarkers (25.9%, n=512) vs. programs that did not (8.4%, n=9,012).

Individual phase transition success rates can be found in **Figure 9**. All four phase transition success rates were much higher for programs incorporating selection biomarkers vs. those not incorporating selection biomarkers. Phase III transition success rates for selection biomarker programs were 76.5% (n=132) vs. only 55.0% (n=1,254) for non-selection biomarker programs - the largest percentage difference among the four phases of development.

There were fewer completed Phase 1 trials that utilized a selection biomarker (43) than those observed in NDA/BLA filings (91). This is likely due to the fact that biomarkers are more commonly used in Phase II and III.

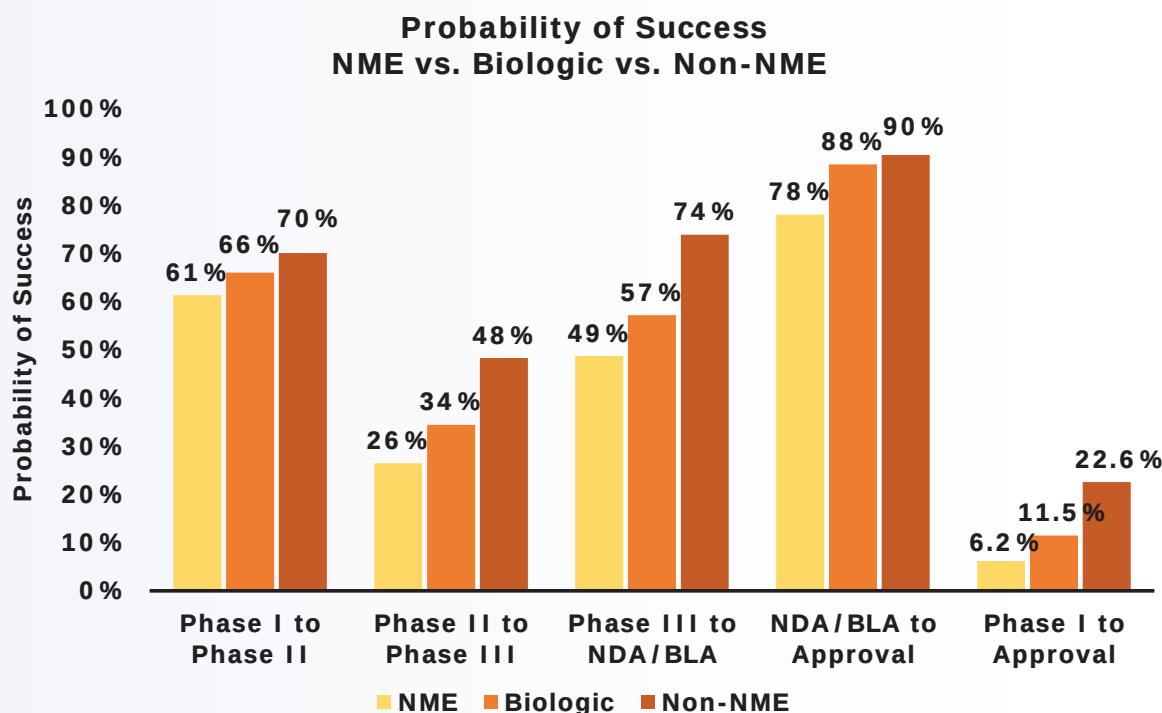
The large differences in Phase II and III transition success rates are quite convincing, quantitatively, of what many drug developers have long argued anecdotally – enrichment of patient enrollment at the molecular level is a more successful strategy than heterogeneous enrollment.

With respect to statistical rigor, while having a smaller number of transitions for programs that utilized a selection biomarker (512) vs. for non-biomarker phase transitions (9,012), when analyzed for statistical significance, all phases, save for Phase I, were found to be statistically significant. This is in large part due to the low n value for Phase I, a clinical phase in which few selection biomarkers are actually used.

Drug Classification and Modality

Drugs in the dataset were annotated by: new molecular entity (NME), non-NME, biologic and vaccine.

Most NMEs are small molecules, although in some cases FDA will designate larger molecules, such as proteins and peptides, as NMEs. When comparing small-molecule NMEs to all NMEs we found very little difference in success rates. The Non-NME classification often includes drugs with the same molecular properties as NMEs, but are frequently reformulations or combinations of approved products. Non-NMEs often use the 505(b)(2) pathway to gain FDA approval. Monoclonal antibodies made up the majority of biologics in the dataset. Other biologics in the dataset included gene therapy, cell therapy, RNAi, and other large molecules. Generic and over-the-counter (OTC) drugs were not included.



Phase Success		Phase I to Phase II		Phase II to Phase III		Phase III to NDA/BLA		NDA/BLA to Approval	
		Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success	Advanced or Suspended	Phase Success
Likelihood of Approval	NME	2236	61.3%	2482	26.5%	731	48.7%	409	78.0%
	Biologic	882	66.0%	883	34.4%	313	57.2%	199	88.4%
	Non-NME	314	70.1%	406	48.3%	398	73.9%	406	90.4%
	Vaccine	95	66.3%	76	32.9%	35	74.3%	32	100.0%
Likelihood of Approval		Phase I to Approval		Phase II to Approval		Phase III to Approval		NDA/BLA to Approval	
		LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA	LOA n	Phase LOA
	NME	5858	6.2%	3622	10.1%	1140	38.0%	409	78.0%
	Biologic	2277	11.5%	1395	17.4%	512	50.6%	199	88.4%
	Non-NME	1524	22.6%	1210	32.2%	804	66.8%	406	90.4%
	Vaccine	238	16.2%	143	24.4%	67	74.3%	32	100.0%

Figure 10. Phase transition success rates and LOA by drug type and class. Top: Chart of phase transition success rates and LOA from Phase I by FDA classification for NME, Biologic, Non-NME. Bottom: Table of phase transition success rates and LOAs for FDA's classifications and vaccines. 'Advanced or Suspended' refers to the total number of transitions used to calculate each success rate, with the n value noted in the text. The LOA n value is the total 'Advanced or Suspended' transitions of all phases used to calculate LOA. 'Phase Success' is the probability of successfully advancing to the next phase, whereas 'Phase LOA' is the probability of FDA approval for drugs in this phase of development.

NMEs were found to have the lowest transition success rates in every phase of development and an LOA from Phase I of just 6.2% (n=5,858). Biologics had almost 2x this LOA (11.6%, n=2,277), as shown in **Figure 10**. The breakout of Monoclonal Antibodies yielded the exact same 11.6% LOA from Phase I (n= 1,258).

Non-NMEs had the highest LOA from Phase I of 22.6% (n=1,524), with transition success rates well above the NME and biologic classifications in every phase. However, many non-NMEs begin development in Phase II or Phase III, so the actual approval rate is likely higher (assuming that successful Phase I outcomes would contribute positively to the LOA from Phase I).

Although a much smaller subset of the modality breakout, vaccines generated a healthy 16.1% (n=238) LOA from Phase I.

Discussion

During the time frame of this study (2006-2015), programs entering clinical development in Phase I were found to have only a one in ten (9.6%) chance of advancing all the way to FDA approval. Although this is an overall probability calculation and does not follow each program from its first trial to final outcome (which is often outside of a 10-year time-frame), we believe that these low success rates for individual drug programs accurately reflect overall industry realities. This is particularly important in the context of cost and time of unsuccessful clinical trials.

Potential factors that may have impacted success rates in this report include:

Clinical and regulatory related:

- Patient population and selection strategy. The impact that a targeted, well-defined patient population can have was observed in the success rates for both selection biomarker usage and rare disease studies.
- Clinical validation of a target, drug class, or mechanism of action. Note that non-NME drugs presented in this report are drugs developed for already approved classes and targets and have 3x higher LOA from Phase I vs. novel NMEs.
- Clinical trial complexity. In chronic, high prevalence diseases, where large heterogeneous patient populations will be treated, additional safety and efficacy studies may be required. These areas have experienced below average LOA from Phase I.

Corporate related:

- Lack of funding. This is a common issue for emerging companies, especially during times of economic stress such as in the years following the global financial of 2008. Programs terminated due to lack of resources or funding would be counted as “suspended” in this study and not differentiated from programs terminated based on disappointing clinical data.
- Commercial decisions and portfolio prioritization. Competition, IP litigation, and other market factors could result in the termination of a program. Internal programs at companies may also compete during pipeline review and prioritization, potentially leading to program termination.

The overall low rates for Phase III programs to successfully transition to an NDA/BLA filing is concerning, as 35% of all R&D spending is now spent on Phase III development, and Phase III trials account for 60% of all clinical trial costs.³ A main contributor to the overall low Phase III transition success rate was found to be Oncology clinical programs. While Oncology remains a very challenging area in which to develop drugs, some more recent successes in immunotherapies give hope that there will be highly successful drug programs in Oncology in coming years.

Outside of Oncology, clinical programs targeting heterogeneous patient populations in chronic, high prevalence indications also contributed to lower overall success rates. For this group, all three clinical-stage transition success rates were lower than the Non-Oncology disease group.

As selection biomarkers are used more frequently in clinical development (presently, they are only being used in a small proportion of studies), phase transition success rates in high prevalence diseases should improve as patient selection improves. The higher success rates for trials run with biomarker-selected patients suggests that the broader industry is already on the right path. For example, Phase III transition success rates in programs utilizing selection biomarkers in the last decade were 76.5% (n=132) compared to only 55.0% (n=1,254) for non-biomarker trials. Experiencing one in four failures (with selection biomarkers) vs. two in four Phase III failures (without biomarkers) could have significant cost implications.

As many rare diseases are identified by specific genetic mutations, it is not surprising that success rates in rare disease indications closely match the success rates observed in clinical trials that utilized selection biomarkers. Phase transition success rates for rare disease candidates and candidates utilizing selection biomarkers were very similar for every stage of development. Transition success rates for each classification, rare disease programs and programs with selection biomarkers, respectively, were; Phase I: 76% and 76.7%; Phase II: 50.6% and 46.7%; Phase III: 73.6% and 76.5%; and NDA/BLA: 89.2% and 94.5%. Both of these specific classifications significantly outpaced the success rates seen for chronic, high prevalence disease drug development at 58.7% in Phase I, 27.7% in Phase II, 61.6% in Phase III, and 87.2% in the NDA/BLA stage.

Greater flexibility with alternative and novel surrogate endpoints, the utilization of adaptive clinical trial design, improved methodologies for assessing patient benefit-risk, and improvements in communication between sponsors and regulators could help improve the success rates reported in this study. Simultaneously, improvements in basic science can enable better success rates. For example, more predictive animal models, earlier toxicology evaluation, biomarker identification and new targeted delivery technologies may increase future success in the clinic.

Advancing industry-wide understanding of the evidentiary standards or considerations governing regulatory acceptance of drug development tools including biomarkers would increase adoption and use of innovative drug development tools, and serve to expedite development and review timelines and improve chances of success.

The ability to utilize these modern approaches to drug development and modern regulatory review processes combined with healthy capital markets supporting private-sector investment will enable biopharmaceutical companies to develop the next generation of innovative medicines.

Methods

Drug Development Programs analyzed in this report track a specific indication for each drug. For example, Rituxan in non-Hodgkin's lymphoma (NHL) qualifies as a different development path than Rituxan in multiple sclerosis (MS). Biomedtracker assigns a unique internal identifier which can be used to isolate all development paths.

In addition to tracking the phase of development, Biomedtracker also assigns "lead" status to certain development paths. This is used to denote the most advanced indication in clinical development for a specific drug. Drugs can only have one lead development program (with some rare exceptions). For example, cancer drugs developed in multiple indications will have the most advanced program assigned as the lead, and the rest as "non-lead". However, in this report we do not differentiate the most advanced programs, and analyze the data on a program/development path level, which more accurately reflects company resource utilization.

Individual Phase Transition Success Rates were calculated as the number of drugs that moved from one phase to the next phase divided by the sum of the number of drugs that progressed to the next phase and the number of drugs that were suspended. The n value associated with the phase transition success rates represent the number of drugs that have advanced plus the number of drugs that have been suspended, which we label as phase transitions. Phase transition Success rates reported in this study were based on transition rates, not necessarily resulting from safety or efficacy data. Transition rates are negatively impacted by early development termination due to commercial and regulatory uncertainty as well as economic and portfolio management decisions.

Biomedtracker further classifies events by phase of development, summarized in the table below:

Biomedtracker phase	Description for purposes of the study
I	Drug is currently in Phase I
I/II, II, IIb	Drug is currently in Phase II
II/III, III	Drug is currently in Phase III
NDA/BLA	Application for approval has been submitted to the FDA and is currently under review
Approved, Withdrawn From Market, Approved (Generic Competition)	Drug has been approved for marketing in the United States
Suspended	Drug is no longer in development
Approved in Europe, Approved in other than U.S./E.U., Development, Development Outside U.S.	The company developing this drug does not plan to market it in the United States

Generic products were not included, but generic manufacturers developing novel investigational drugs were represented.

Likelihood of Approval (LOA) denotes the probability of reaching FDA approval from the current phase, and is also expressed as a percentage. LOA is calculated as the product of each Phase Success probability leading to FDA approval. The n value associated with LOA is the sum of the n values for each Phase Success included in the LOA calculation.

For example, if a drug is currently in Phase II, and the phase success for Phase II is 50% (n=10), Phase III is 50% (n=10), and FDA Approval is 50% (n=10), then the LOA for the Phase II drug would be 12.5% ($50\% \times 50\% \times 50\% = 12.5\%$, n=30).

Data Source for Drug Program Transitions. Data used for this study were extracted from Biomedtracker using a Probability of Technical Success (PTS) tool, which identified all 'Advanced' and 'Suspended' drugs by development phase from January 1, 2006 to December 31, 2015. Biomedtracker, a subscription-based product of Informa, tracks the clinical development and regulatory history of investigational drugs to assess their Likelihood of Approval (LOA) by the FDA. Biomedtracker is populated in near real-time with updated information from press releases, corporate earnings calls, investor and medical meetings and numerous other sources. These data are recorded in BioMedTracker and tagged with a date. BioMedTracker also uses other sources, including regular communication with companies conducting clinical trials, to ensure accuracy and timeliness of the data.

Drug Classification Methods. Biomedtracker records FDA classification (i.e. new molecular entity (NME), non-NME, biologic, or vaccine) as well as the biochemical profile (e.g. small molecule, monoclonal antibody, peptides, natural proteins, antisense, vaccine, etc.). Biologics, as defined by FDA, can be sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues.

Sub-Indications. Drilling down into sub-indications within each major disease area has limitations due to lower n values for each phase. The statistical significance of the results must be taken into account when comparing data from low sample sizes. Although this study is over a 10-year period, some sub-indications had a limited number of Phase III programs completed or NDA/BLA filings submitted. For example, because AML had four drugs submitted for FDA approval, and no wins, the success rate for AML at the NDA/BLA stage is 0% (n=4). That also means that the LOA calculation for AML yields 0% (n=103), due to the compounded approach of multiplying individual phase probabilities to arrive at the overall LOA. With that caveat in mind, it is best to approach sub-indications starting with the NDA/BLA filing phase to assess n values and % success.

Data Source for Selection Biomarkers. Selection biomarkers are gene products used as inclusion or exclusion criteria for enrolling patients into clinical studies. The biomarker subject selection data used for this study were extracted from BiomarkerBase, which identifies selection biomarkers described in clinical trials posted at ClinicalTrials.gov. BiomarkerBase is a subscription-based service from Amplion that tracks selection biomarker usage in clinical trials, drug labels, and tests (including laboratory-developed, FDA-cleared, and FDA-approved tests). BiomarkerBase is updated weekly with information from these sources and publications, using supervised machine learning algorithms for natural language processing (Amplion BiomarkerEngine) to identify selection biomarkers. BiomarkerBase includes primarily human genes and proteins. Other diagnostic measurements, including clinical blood chemistry, liver enzymes, white blood cell count, heart rate, blood oxygenation, blood glucose, clotting times, etc. are not included in BiomarkerBase.

Comparison with Previous BIO/Biomedtracker Study. The Biomedtracker database has expanded since our original publication in Nature Biotechnology, January 2014.¹ The first study contained 5,820 phase transitions from 2003-2011. The current study contains 9,985 transitions from 2006-2015 (10 years). This more recent finding for overall LOA success rates falls within the same statistical range as our previous report (near 10.4%, n=5,820 for 2003-2011).^{1,2} While the more recent study captures four additional years (2012-2015), it begins in 2006 and thus cuts 2003-2005 data, leaving a 10-year window for evaluation. Importantly, there are 4,165 more transitions in the current dataset. Such broad sample size comparisons makes it very difficult for significant changes to be found in overall rates. To see significant change would require more than just a few disease areas to experience profound improvements in productivity. For example, the impressive success rates found in Hematology might need to be seen in the larger groups such as Oncology or Neurology to move the needle. Narrowing the time-frame to detect improvements, can lead to program biases as R&D timelines are typically closer to a 10-year time-frame and not less.

Lead Drug vs. Non-Lead. In our previous report, we had included “Lead” drug success rates.¹ That allows us to answer the question: “What is the probability that a drug will reach approval for any indication?” However, the Lead program analysis will not represent the true costs, both monetary and time, that is required for approval. Furthermore, it can be a source of confusion in that it refers not to a company’s lead program, but rather the most advanced indication for a given drug. Lead indication status is constantly changing within the database through time as programs fail and secondary indication then become the Lead indication. For this reason, the current study focuses on each development path to answer the question: “What is the probability that a drug developed for a specific indication will reach approval?”

For those interested in the Lead indication success rates, the overall Lead success rate was 16.8% (n = 5,511), 1.7x higher than the 9.6% reported for individual development paths. This is a slightly wider difference than our previous finding (for 2003-2011) of 15.3% for the Lead indication. As the spread between Lead and subsequent individual indication programs widens, it could be argued that more R&D is required (across multiple indications) to reach final approval of a chemical entity in at least one of its indications.

References

1. Hay, M., Thomas, D., John L Craighead, J.L., Economides, C., Rosenthal, J. Clinical development success rates for investigational drugs. *Nature Biotechnology* 32, 40-51 (2014).
2. Thomas, D., Wessel, C. Emerging Therapeutic Company Investment and Deal Trends 2006-2016. <http://www.bio.org/iareports>
3. Pharmaceutical Research and Manufacturers of America. Annual Report 2011. PhRMA website [online], http://www.phrma.org/sites/default/files/159/phrma_2011_annual_report.pdf (2011).
4. Global Genes Rare Disease Facts: <http://globalgenes.org/rare-diseases-facts-statistics>
5. Amplion Inc. Market Trends for Biomarker-Based IVD Tests (2003-2014). <http://www.amplion.com/download-the-commercial-trends-in-ivds-report> (Amplion 2015).
6. BiomarkerBase: <https://biomarkerbase.com/>

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Appendix BOOTH02

FROM THE ANALYST'S COUCH

Oncology's trials

Bruce Booth, Robert Glassman and Philip Ma



Degas couch, 'Rehearsal', by Heather Sussman © 2002

The oncology market has witnessed remarkable growth during the past five years and is poised for even greater growth during the next three years. The total oncology market is expected to reach more than US \$32 billion in size by 2005, driven by factors including a continued trend towards aggressive chemotherapy, active patient populations that demand access to the latest therapies, and continued favourable pricing due to high unmet need. Moreover, nearly all of the major pharmaceutical companies have active oncology development programmes, and for biotech firms, oncology projects dwarf all other R&D programmes.

Challenges from attrition

In spite of all this positive momentum for the oncology market, pharmaceutical and biotech companies who play in this area face the crucial issue of late-stage clinical attrition. Even with more than 500 oncology compounds in development, only a few achieve regulatory approval each year and there are only ~90 approved oncology drugs in the US today. A number of high-profile clinical and regulatory setbacks, such as the cases of gefitinib (Iressa; AstraZeneca) and cetuximab (Erbix; Imclone), highlight the challenges that oncology drug candidates are facing. The dramatic unpredictability of single-arm, uncontrolled Phase II trials in cancer helps explain why anti-cancer drug development is so challenging. Although oncology projects have higher average success rates than other therapeutic areas in early-stage trials (that is, Phase I and II), these projects have a lower average success rate than other therapeutic areas at Phase III. Oncology projects are riskier than those in other therapeutic areas, precisely at the stage of clinical development in which costs are highest. Moreover, early development trials do not seem to be very predictive of success rates for later development, which could mean that the industry might soon face a big series of disappointments in the form of failed drug candidates.

Causes of high attrition

Several key factors drive the high rate of attrition we are seeing with oncology compounds: market pressures, challenges with

the underlying science and changes in the regulatory environment. On the market side, companies are under significant pressure to reach for the broadest possible label on first regulatory approval to capture a broad market. As such, many initial label applications target one or more of the 'big four' tumour types: breast, prostate, lung and colon cancer. The challenge in doing this is that the standard clinical practice for these tumours often involves multiple drug cocktails of cytotoxic chemotherapy agents. So, for new therapies, clinical trials need to show incremental improvement over these multiple existing chemotherapy regimens, which can be difficult to demonstrate, especially with smaller size trials.

Scientific and regulatory challenges

The nature of the basic science of oncology also leads to high attrition rates for anticancer compounds. With the rapid accumulation of new knowledge, there are more and more novel approaches to anti-cancer drug development. Indeed, more than 40% of the compounds in development for cancer are directed against novel or 'unprecedented' mechanisms, and almost 70% of the drug targets that are being investigated in discovery are unprecedented. In earlier research, we had shown that novel approaches had significantly higher risks than tried-and-tested approaches, and, notably, some of the more high-profile recent setbacks in oncology have involved novel mechanisms, such as drugs targeting signal transduction (for example, RAS farnesylation). For every major success such as bevacizumab (Avastin; Genentech) in colorectal cancer, there have been many more failures.

The last factor for high attrition rates in oncology has been a growing conservatism within the US FDA and other regulatory approval bodies. In the past, when there were fewer available cancer therapies, the FDA often accepted surrogate endpoints (such as tumour reduction). Today, with better available treatments, the FDA has moved more aggressively towards clinical endpoints such as survival, which are exceedingly tough to prove in populations with refractory, progressive tumours — the types that are often the focus of clinical trials today. Not surprisingly, these higher regulatory hurdles increase the

likelihood of clinical attrition. Given recent public pressure, however, the FDA could be easing its stance. For example, it recently approved gefitinib with only clinical response and no survival benefit in lung cancer.

Future of oncology drug development

Given the market, science and regulatory drivers behind attrition in oncology drugs, how can oncology drug development move forward? First of all, biotech and pharmaceutical companies should consider pursuing initial indications in well-defined, potentially niche tumours that will allow for a potentially lower-risk path to get regulatory approval. Once the drug has received initial regulatory approval, there are many other opportunities to expand indications through additional post-marketing trials. About 70% of cancer drugs are used off label — for example, thalidomide, which although not even approved as a cancer therapeutic is a dominant drug in myeloma and melanoma and is being tested in renal and prostate cancer.

There is a significant opportunity for concurrent research into biomarkers at the same time that the target mechanism is being explored. Tissue imaging, in particular, could be a fruitful source of biomarkers given the advances in magnetic resonance imaging and positron emission tomography imaging. As a caveat, however, biochemical and molecular markers have not yet proven to be predictive of clinical response; for example, vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) expression do not correlate with response to the appropriate antagonists.

Finally, companies should consider other Phase II trial designs that are more predictive of Phase III success. Examples include randomized Phase II studies, Bayesian approaches, studies in tough, defined populations such as the truly refractory, and uses of 'easier' endpoints such as time to progression¹. A key challenge for both industry and the regulatory agencies in the development and approval of combinations of multiple novel cytotoxics and cytostatics in patients with minimal residual disease, the exact scenario in which beneficial outcomes are most likely, but where proving these benefits can be complex. ▶

HIGHLIGHTS

FROM THE ANALYST'S COUCH

Market indicators

Phase II trials in oncology do not show significant predictability for Phase III outcomes (TABLE 1). A comparison of trial success rates across different therapeutic areas again shows the poor correlation between Phase II and Phase III success rates for oncology trials (FIG. 1). One of the key drivers for the high clinical attrition rates for oncology compounds is the high proportion of unprecedented targets that these compounds are directed against (FIG. 2). Historically, compounds directed against unprecedented targets have a higher level of clinical attrition than compounds against targets with a precedent. The total oncology market is expected to reach more than US \$32 billion by 2005 (FIG. 3).

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1. Fossa, S. & Skovlund, E. Selection of Patients May Limit the Generalizability of Results from Cancer Trials. *Acta Oncologica*. **41**, 131–137 (2002).
2. Stadtmauer, E. *et al.* Conventional dose chemotherapy compared with high dose chemotherapy plus autologous hematopoietic stem cell transplantation for metastatic breast cancer. *N. Engl. J. Med.* **342**, 1069–1076 (2000).

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Table 1 | **Oncology trial examples**

Promising Phase II studies	Negative Phase III studies
Multiple second- and third-generation lymphoma regimens showed doubling of responses and survival compared with first generation CHOP regimen.	SWOG randomized study comparing CHOP with second generation ProMACE-CytaBOM or MACOP-B showed no difference in CR, time to treatment failure, or OS.
Phase II studies of angiogenesis inhibitor SU5416 showed better responses and survival compared with historic controls in advanced colorectal cancer.	A large phase III study of standard chemotherapy with or without the angiogenesis inhibitor SU5416 in the treatment of patients with advanced stage colorectal cancer did not achieve its endpoints.
Several Phase II studies from late 1980s showed higher response rates (73–100%) and 7–18% DFS post-five-years for high-dose chemotherapy and stem cell transplantation for metastatic breast cancer.	ECOG study ² reported no differences in survival or time to disease progression between autologous stem cell transplant with high dose chemotherapy and conventional chemotherapy.

CR, complete response; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; SWOG, South Western Oncology Group

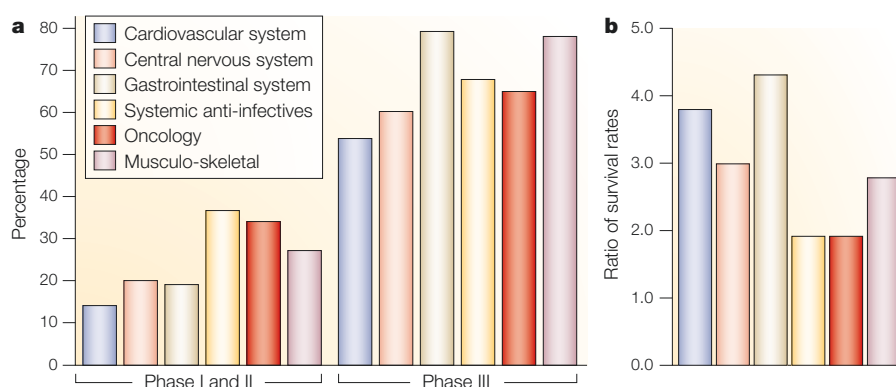


Figure 1 | **Project survival rates.** **a** | Comparison of rates through Phases I/II and Phase III/registration between 1991 and 2000 at fifteen top pharmaceutical companies. Projects without updated data after five years were considered failures. **b** | The low ratio of Phase II/registration to Phase I/II success rates for both systemic anti-infectives and oncology projects, is indicative of the low predictive power of early stage trials in these two areas. Source: PBJ Publications Phamaprojects; US FDA/Center for Drug Evaluation Research; McKinsey analysis.

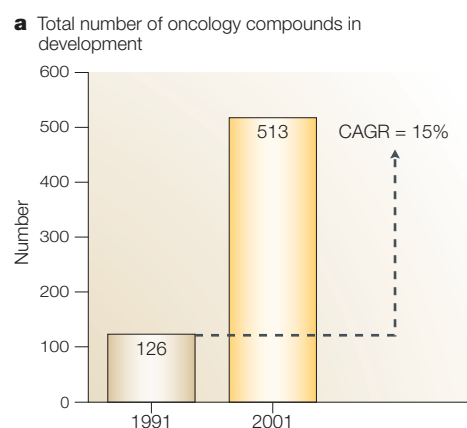


Figure 2 | **Target mechanisms for oncology development projects.** Roughly 40% of compounds in development are novel. In the period 1996–2001 only nine novel targets had compounds against them approved, whereas today 15 novel targets are being tested in Phase III trials. CAGR, compound annual growth rate. Source: PBJ Publications Phamaprojects; US FDA/Center for Drug Evaluation Research; McKinsey analysis.

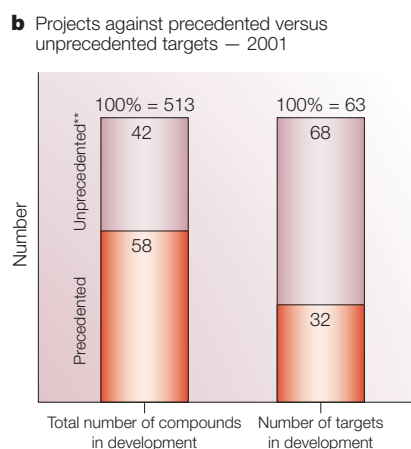
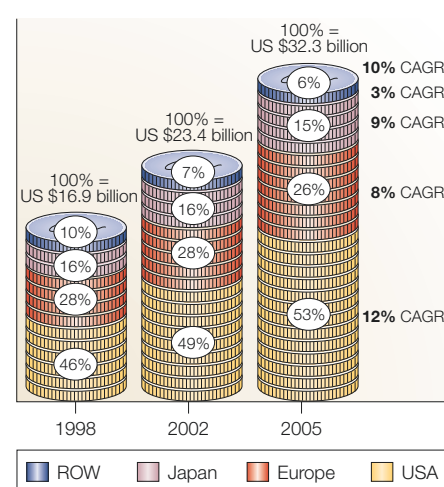


Figure 3 | **Expected growth of global oncology market.** CAGR, compound annual growth rate.

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Appendix CAVANNA02

Modified FOLFIRINOX for unresectable locally advanced/metastatic pancreatic cancer. A real-world comparison of an attenuated with a full dose in a single center experience

This article was published in the following Dove Press journal:
OncoTargets and Therapy

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Purpose: Metastatic pancreatic adenocarcinoma has a very poor prognosis. Although irinotecan, oxaliplatin and leucovorin-modulated fluorouracil (FOLFIRINOX) significantly increases survival in advanced pancreatic cancer, compared to employing only gemcitabine (GEM), toxicities have tempered enthusiasm for its use.

Methods: This study retrospectively analyses the real-world clinical practice with full and attenuated doses of FOLFIRINOX in unselected patients with locally advanced unresectable or metastatic pancreatic cancer, treated at an Italian general hospital. Efficacy, tolerability, and toxicity were evaluated, and overall survival (OS) and progression-free survival (PFS) were estimated by Kaplan–Meier method.

Results: Fifty consecutive patients with advanced (13) or metastatic (37) pancreatic adenocarcinomas were treated with FOLFIRINOX at the Medical Oncology Unit, Piacenza General Hospital, North Italy. The first enrolled consecutive 18 patients (36%) of this series started the treatment with a full dose of the regimen, while the subsequent 32 (64%) consecutive patients received dose attenuation (–20% bolus fluorouracil and –25% irinotecan). In the entire group, the response rate, median OS, and median PFS were 30%, 10.1 months, and 5.6 months, respectively, with no differences in objective response in the 32 patients that received an attenuated dose compared with the 18 patients receiving a full dose of chemotherapy. However, neutropenia, anemia, fatigue, and vomiting were statistically increased in the 18 patients receiving a full dose compared with the 32 patients receiving an attenuated dose of FOLFIRINOX ($p < 0.05$).

Conclusion: This study demonstrates the efficacy and tolerability of modified FOLFIRINOX in advanced and metastatic pancreatic cancer.

Keywords: metastatic pancreatic cancer, locally advanced pancreatic cancer, FOLFIRINOX, chemotherapy

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Introduction

Pancreatic cancer is a major cause of cancer-related mortality in western countries and it is projected to emerge as the second leading cause of cancer-related deaths in the United States by 2030.¹ Its prognosis is extremely poor, with a 5-year survival rate for all patients with pancreatic adenocarcinoma of approximately 6–8%.^{2–5} The vast majority of patients (80–90%) present with incurable metastatic or locally advanced unresectable disease.¹ Gemcitabine (GEM) became the standard of care

after a randomized trial that demonstrated an improvement in median overall survival (OS) compared with bolus of fluorouracil.⁶ The trial also evaluated the impact of GEM on “clinical benefit response” with an increase in clinical benefit responses in favor of GEM. Although well tolerated, the efficacy of single-agent GEM is marginal with a median OS of 5.65 months and a 1-year OS rate of 18% in patients with advanced pancreatic carcinoma.⁶ GEM has been evaluated in combination with a variety of cytotoxic and targeted agents, but no meaningful gains were observed in OS.^{7–14} Over the past few years, additional treatments have become available for patients with pancreatic cancer. In 2011, Conroy et al demonstrated that irinotecan, oxaliplatin, and leucovorin-modulated fluorouracil (FOLFIRINOX) was associated with a significant improvement in response rate (RR), progression-free survival (PFS), and clinically meaningful improvement in OS from 6.8 to 11.1 months when compared with GEM alone in metastatic pancreatic cancer.¹⁵ However, although patients’ quality of life improved compared with treatment with GEM alone, FOLFIRINOX was also associated with significant toxicities, such as neutropenia, diarrhea, and peripheral neuropathy. Some prospective and retrospective studies have confirmed the data of this trial in terms of OS, PFS, and safety, but the significant toxicities of FOLFIRINOX have tempered enthusiasm for a widespread use of FOLFIRINOX in community and academic practices.^{16–19} It must be emphasized that nanoparticle albumin-bound paclitaxel (nab-*P*) in combination with GEM has been approved for the treatment of advanced pancreatic cancer; this schedule is an equally valid front-line option for patients with metastatic pancreatic cancer and consists in the combination of GEM and nab-*P*.²⁰ Some retrospective studies recently reported the comparison of treatment patterns, resource utilization, and cost of care in patients with metastatic pancreatic cancer treated with FOLFIRINOX or GEM plus nab-*P*.^{21,22} These studies compared, however, full-dose FOLFIRINOX and not reduced dose, and they concluded that patients treated with nab-*P* plus GEM vs FOLFIRINOX had similar treatment duration, but lower costs of outpatient prescriptions of treatment administration and of supportive care. Lower supportive care costs in the nab-*P* plus GEM cohort were mainly driven by lower utilization of pegfilgrastim and anti-emetics. Toxicity-related costs and drug acquisition costs should be considered when evaluating total cost of care. In addition, nanoliposomal irinotecan was approved by the FDA in combination with 5-fluorouracil (5-FU) and

folinic acid for the treatment of patients with pancreatic cancer after disease progression following GEM-based therapy.²³ The current standard of care for metastatic pancreatic cancer patients with a good performance status is either FOLFIRINOX or GEM plus nab-*P*.^{15,20,24} However, more recently, some prospective and retrospective studies evaluated the efficacy and the safety profile of modified FOLFIRINOX in advanced/metastatic pancreatic adenocarcinoma.^{24–32} To evaluate the real-world clinical practice with FOLFIRINOX, we conducted a retrospective study of 50 patients with advanced/metastatic pancreatic cancer; in 32 of these patients (64%) the treatment was planned with an attenuated dose, while in 18 cases (36%) the treatment was planned with full dose. This study was done at the Medical Oncology Unit, Piacenza General Hospital (North Italy). The efficacy and the toxicities of these schedules were assessed and reported.

Material and methods

We retrospectively analyzed the medical records of all patients with locally advanced or metastatic pancreatic cancer treated with FOLFIRINOX as first-line chemotherapy between July 2013 and July 2017 at the Medical Oncology Department, Piacenza General Hospital (North Italy). Patients were considered eligible if they have received at least one cycle of FOLFIRINOX. This study was a retrospective cohort, single-institution analysis. Its objectives were to evaluate the efficacy and safety of FOLFIRINOX in unselected patients with advanced/metastatic pancreatic cancer in a general hospital. The study was approved by the Institutional Review Board of Piacenza hospital and conducted according to the Helsinki Declaration. Written informed consent was obtained from each patient that underwent both full and attenuated doses of FOLFIRINOX. In addition, all the patients of this study signed written informed consent allowing research use of their clinical data. Patient characteristics, toxicities, RR, PFS, and OS were evaluated. The patients were not randomized. Standard practice for the first 18 patients was to start treatment using full-dose FOLFIRINOX, consisting of 85 mg of oxaliplatin per square meter given as a 2 hrs intravenous infusion, immediately followed by leucovorin at dose of 400 mg per square meter, delivered as a 2-hr intravenous infusion, with the addition, after 30 mins, of irinotecan at a dose of 180 mg per square meter, given as a 90-min intravenous infusion. This treatment was immediately followed by fluorouracil at a dose of 400 mg per square meter administered by intravenous bolus, followed by a continuous intravenous infusion of 2,400 mg per square meter over a 46-hr

period every 2 weeks. The premedication regimen consisted of intravenous ondansetron and dexamethasone and prophylactic treatment with atropine was given to prevent cholinergic syndrome. Granulocyte-Colony Stimulating Factor (G-CSF) was used as a secondary prophylaxis, when required. Cycles were planned for 6 months (12 cycles), and were stopped before the 12 planned cycles, for tumor progression or occurrence of unacceptable toxicity. After the first 18 consecutive patients started with full dose of this regimen, a dose reduction was made with this percentage: bolus-fluorouracil reduced by 20% and irinotecan reduced by 25%. The regimen was changed on the basis of previous report suggesting that modest dose attenuation was associated with good tolerability and with efficacy comparable with results reported by Conroy T et al.^{15,32}

All the patients were evaluated for toxicities with history, clinical examination, performance status, complete blood count, and metabolic panel with liver and kidney tests. Response assessment with imaging ultrasound and computerized tomography (CT) was obtained every 4–6 cycles of treatment using the Response Evaluation Criteria in Solid Tumors guidelines (RECIST, version 1.1).³³ Patients who received chemotherapy for locally advanced/non resectable, but non-metastatic cancer underwent CT scan for response assessment. They were evaluated by a multidisciplinary team with surgeons and radiologists to establish the possibility of the surgical resection. All patients receiving the two schedules of FOLFIRINOX were eligible for toxicity analysis; patients were followed for PFS and OS.

OS was calculated from the start of the treatment to the date of death. PFS was calculated from the start of FOLFIRINOX to the date of radiographic progression (local or metastatic), or death. PFS and OS estimates were obtained using Kaplan–Meier method. Both OS and PFS were calculated for entire group and for the subgroups: 1) locally advanced; 2) metastatic pancreatic cancer; 3) patients that received full dose; and 4) patients that received attenuated dose of chemotherapy.

Results

Between July 2013 and July 2017, 50 patients with advanced/metastatic pancreatic adenocarcinoma were treated with FOLFIRINOX at the Medical Oncology Unit, Piacenza General Hospital (North Italy). There were 13 patients with locally advanced unresectable disease and 37 with metastatic disease. All the patients were pathologically diagnosed with percutaneous (37 patients) or endoscopic (13 patients) ultrasound-guided biopsy. The median

age was 65 years (range, 40–76), 24 patients were female (48%) and 26 (52%) men. The patient and disease characteristics are shown in Table 1. Eighteen patients received a full-dose FOLFIRINOX and 32 an attenuated dose; performance status was 0–1 in 42 cases (84%) and 2 in the remaining 8 patients (16%). Pancreatic tumor location was in the head in 27 patients (54%), in the body in 17 cases (34%), and in the tail in 6 cases (11.1%). The disease status (metastatic/locally advanced, Eastern Cooperative Oncology Group performance status, tumor location, site of metastases, age, and sex) did not differ between the two groups (Table 1). The entire group of the 50 patients received a median of 8 cycles of FOLFIRINOX (range 1–12). The mean number of cycles performed was 9 (range 3–12) in the group of modified and 7 (range 1–12) in the group of standard FOLFIRINOX. Nine patients, 4 with modified and 5 with standard therapy received <4 cycles. One of the 18 patients receiving a full dose suspended the FOLFIRINOX chemotherapy after the first cycle because of a prolonged pancytopenia with febrile neutropenia. RR in locally advanced and metastatic disease are shown in Table 2. In the whole cohort, no patient showed a complete response and 15 patients (30%) had a partial response with an overall RR of 30%, while a further 8 patients (16%) showed stable disease. No differences in RR were registered between the two groups of patients receiving attenuated dose or full dose of chemotherapy (Table 2). The OS and PFS are shown in Table 3 and Figure 1A and B. For the entire cohort of patients, the median OS was 10.07 months and the median PFS was 5.63 months; in patients with locally advanced disease, the median OS was 11.47 months while median PFS was 6.27 months. There were no significant differences in OS (10.52 vs 10.07 months) and PFS (5.7 vs 6.13 months) in the 32 patients who received attenuated dose chemotherapy compared with the 18 patients that received a full dose.

Treatment-related toxicities are summarized in Table 4. Any-grade neutropenia was recorded in 28 patients (56%); in 16 (32%) it was grade 3/4, with febrile neutropenia in 3 patients (6%). Grade 3/4 thrombocytopenia was registered in 3 patients (6%). Grade 3/4 anemia was registered in 6 patients (12%). Non-hematologic toxicities were: fatigue in 30 patients (60%) and with grade 3/4 in 11 patients (22%); diarrhoea grade 1/2 in 13 (26%) and 3 cases with grade 3/4 (6%), vomiting in 32 cases (64%), with grade 3/4 in 4 patients (8%), and peripheral sensory neuropathy in 10 patients (20%), with grade 3/4 in 4 patients (8%). There were no deaths related to chemotherapy

Table 1 Characteristics of the 50 patients with locally advanced/metastatic pancreatic cancer, 18 patients receiving a full dose compared with the 32 patients receiving an attenuated dose

Characteristics	Patients n (%)		Full-dose patients (%)		Attenuated dose patients (%)		p-value ^a
	n=50	(100)	n=18	(36)	n=32	(64)	
Age, median (range)	65 (40–76)		65 (40–76)		65 (41–75)		
Sex	24	(48)	8	(44.4)	16	(50)	0.77
Male	26	(52)	10	(55.6)	16	(50)	
Female							
Stage	37	(74)	14	(77.8)	23	(71.9)	0.75
Metastatic cancer	13	(26)	4	(22.2)	9	(28.1)	
Advanced unresectable cancer							
ECOG performance status							
0	25	(50)	8	(44.4)	17	(53.1)	0.77
1	17	(34)	7	(38.9)	10	(31.3)	0.76
2	8	(16)	3	(16.7)	5	(15.6)	1
Tumor location							
Head	27	(54)	9	(50)	18	(56.3)	0.77
Body	17	(34)	7	(38.9)	10	(31.2)	0.76
Tail	6	(12)	2	(11.1)	4	(12.5)	1
Sites of metastasis							
Liver	28	(56)	12	(66.7)	16	(50)	
Lymphnode	18	(36)	8	(44.4)	10	(31.6)	
Lung	17	(34)	7	(38.9)	10	(31.6)	
Peritoneum	20	(40)	8	(44.4)	12	(37.5)	
Biliary stent	16	(32)	6	(33.3)	10	(31.6)	

Note: ^ap-value calculated using Fisher's exact test.

Table 2 Objective response in the 50 patients with locally advanced/metastatic pancreatic cancer, 18 patients receiving a full dose compared with the 32 patients receiving an attenuated dose

Objective response	Patients n (%) (total=50)	p-value ^a
CR (All patients=50)	0 (0)	1
Patients receiving an attenuated doses (n=32)	0 (0)	
Patients receiving a full doses (n=18)	0 (0)	
PR (All patients=50)	15 (30)	0.52
Patients receiving an attenuated doses (n=32)	11 (34.4)	
Patients receiving a full doses (n=18)	4 (22.2)	
SD (All patients=50)	8 (16)	0.69
Patients receiving an attenuated doses (n=32)	6 (18.8)	
Patients receiving a full doses (n=18)	2 (11.1)	
PD (All patients=50)	20 (40)	1
Patients receiving an attenuated doses (n=32)	13 (40.6)	
Patients receiving a full doses (n=18)	7 (38.9)	

Note: ^ap-value calculated using Fisher's exact test.

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 3 OS and PFS in the 50 patients with locally advanced/metastatic pancreatic cancer, 18 patients receiving a full dose compared with the 32 patients receiving an attenuated dose

Patients	Median OS (range) (months)	Median PFS (range) (months)
All patients (n=50)	10.07 (0.53-28.2)	5.63 (0.4-21.93)
Receiving an attenuated doses (n=32)	10.52 (0.53-28.2)	5.70 (0.4-21.93)
Receiving a full doses (n=18)	10.07 (1.0-24.3)	6.13(0.77-21.5)
Metastatic (n=37)	10.07 (0.53-28.2)	5.63 (0.4-21.93)
Receiving an attenuated doses (n=23)	10.52 (0.53-28.2)	5.70 (0.4-21.93)
Receiving a full doses (n=14)	10.90 (1.0-18.7)	6.13 (0.77-14.43)
Locally advanced (n=13)	11.47 (4.6-24.3)	6.27 (1.3-21.5)
Receiving an attenuated doses (n=9)	11.47 (4.6-15.6)	5.98 (1.3-12.87)
Receiving a full doses (n=4)	12.83 (15.9-24.3)	7.10 (7.3-21.5)

Abbreviations: OS, overall survival; PFS, progression-free survival.

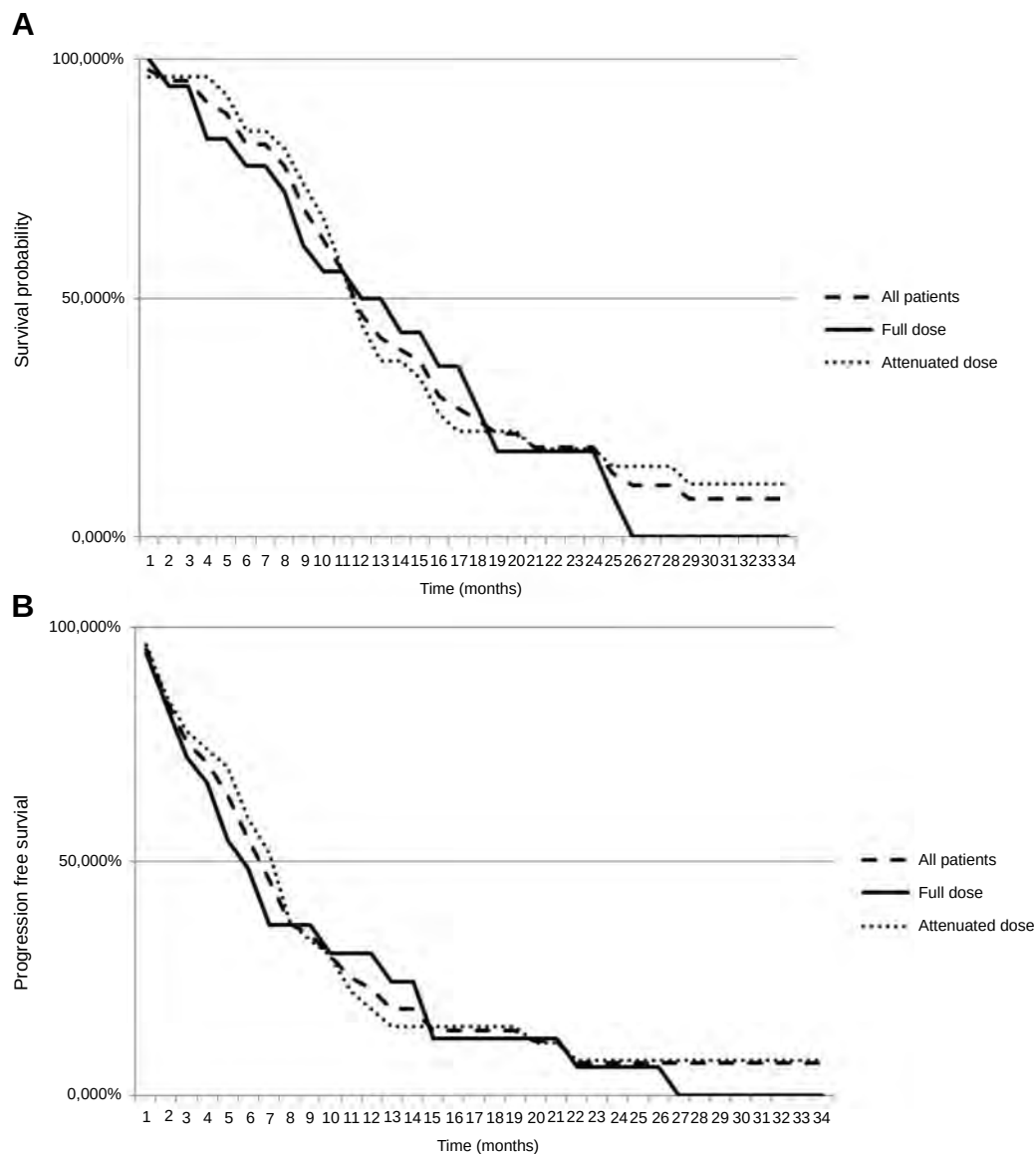


Figure 1 (A) Kaplan-Meier, overall survival. (B) Kaplan-Meier, progression-free survival.

Table 4 Treatment-related toxicities in the 50 patients with locally advanced/metastatic pancreatic cancer, 18 patients receiving a full dose compared with the 32 patients receiving an attenuated dose

Toxicity	Any grade n (%)	Grade 3/4 n (%)	p-value ^a
Neutropenia (All patients=50) Receiving an attenuated dose (n=32) Receiving a full dose (n=18)	28 (56) 15 (46.9) 13 (72.2)	16 (32) 6 (18.8) 10 (55.6)	0.01
Febrile neutropenia (all patients=50) Receiving an attenuated dose (n=32) Receiving full dose (n=18)	3 (6) 2 (6.3) 1 (5.6)	3 (6) 2 (6.3) 1 (5.6)	1
Thrombocytopenia (all patients=50) Receiving an attenuated dose (n=32) Receiving a full dose (n=18)	17 (34) 11 (34.4) 6 (39.3)	3 (6) 1 (3.1) 2 (11.1)	0.29
Anemia (all patients=50) Receiving an attenuated dose (n=32) Receiving a full dose (n=18)	29 (58) 13 (40.6) 16 (88.9)	6 (12) 1 (3.1) 5 (27.8)	0.02
Fatigue (all patients=50) Receiving an attenuated dose (n=32) Receiving a full dose (n=18)	30 (60) 14 (43.8) 16 (88.9)	11 (22) 3 (9.4) 8 (47.1)	0.01
Diarrhoea (all patients=50) Receiving an attenuated dose (n=32) Receiving a full dose (n=18)	13 (26) 8 (25) 5 (27.8)	3 (6) 1 (3.1) 2 (12.5)	0.29
Vomiting (all patients=50) Receiving an attenuated dose (n=32) Receiving a full dose (n=18)	32 (64) 15 (46.9) 17 (94.4)	4 (8) 0 (0) 4 (23.5)	0.01
Peripheral sensory neuropathy (all patients=50) Receiving an attenuated dose (n=32) Receiving a full dose (n=18)	10 (20) 5 (15.6) 5 (29.4)	4 (8) 1 (3.1) 3 (17.6)	0.13

Note: ^ap-value calculated using Fisher's exact test.

toxicities. The incidence of grade 3 or 4 neutropenia (55.6% vs 18.8%, $p=0.01$), anemia (27.8% vs 3.1%, $p=0.02$), fatigue (47.1% vs 9.4, $p=0.01$), and vomiting (23.5% vs 0%, $p=0.01$) was significantly increased in the 18 patients receiving a full dose compared with the 32 patients treated with an attenuated dose of FOLFIRINOX. Fifteen patients (33.3%) had biliary stents in situ at the time of treatment with FOLFIRINOX and three cases of cholangitis were registered. G-CSF (Filgrastim) was given a secondary prophylaxis in the 16 patients (32%) who developed grade 3 or 4 neutropenia after the first or subsequent cycles. The G-CSF was given in 9 of the 18 patients (50%) treated with a full dose of the regimen and in 7 of the 32 patients treated with an attenuated dose (21.9%). The difference was not statistically significant ($p=0.06$). Only one (7.7%) of the 13 patients with locally

advanced pancreatic cancer underwent surgical exploration with curative intent. However, peritoneal micrometastasis prevented surgical treatment.

At the time of last follow-up, 24 patients (48%) had received one or more further lines of palliative chemotherapy. Of these 24 patients, 16 patients (66.7%) received GEM/nab-P, 4 patients (16.7%) received capecitabine, and 4 patients (16.7%) received GEM. After completing treatment with FOLFIRINOX, 2 patients received consolidation radiotherapy (54 Gy in 30 fractions) with concomitant capecitabine.

Discussion

The purpose of this study was to evaluate the efficacy and safety of a FOLFIRINOX regimen in advanced/metastatic pancreatic cancer in an Italian general hospital. Despite the

majority of the patients treated at our institution receiving an attenuated dose of FOLFIRINOX, our findings suggest that the efficacy was not compromised by this reduction, with a significant improvement in toxicity. In a recently reported prospective Phase II study, irinotecan and bolus fluorouracil were reduced by 25% and a decrease in adverse events (AEs) without negative impact on efficacy was registered.³¹ According to these results, some authors reported a modified regimen of FOLFIRINOX, resulting in lower hematological and non-hematological toxicity rates, with comparable efficacy outcomes.^{25–32} It has been demonstrated that in a modified FOLFIRINOX regimen, to preserve optimal RR and disease control rate in advanced/metastatic pancreatic cancer, the recommended values of cumulative relative dose intensity (CRDI) are for FOLFIRINOX >70% and 55%, respectively, and if a CRDI is >80%, primary G-CSF prophylaxis is recommended.²⁶ The RR of 30% in our patients was not significantly different from the RR of 31.8% in the historical FOLFIRINOX-treated patients reported by Conroy et al, and was comparable with the data reported by other retrospective and prospective series.^{15,25–32} Survival outcomes, with an OS of 10.1 months and a PFS of 5.6 months in patients with metastatic pancreatic cancer, were also comparable with the data reported in the prospective randomized trial.¹⁵ Our results support the assumption that these outcomes can be achieved outside of a clinical study, also in a general hospital in the real-world practice. As expected, the outcomes for patients with locally advanced pancreatic cancer were better than those for patients with metastatic disease, with a median OS of 11.47 months and a median PFS of 6.3 months. Again, this was comparable with previously published retrospective and prospective series.^{25–32}

However, although FOLFIRINOX is associated with a significant increase in RR and OS in metastatic pancreatic cancer compared to GEM alone, we note that the toxicities of FOLFIRINOX have tempered enthusiasm for a full-dose use in community and academic centers.³¹ In the present study, the majority of patients with advanced/metastatic pancreatic cancer were treated with an attenuated dose of FOLFIRINOX; this choice was based also on the results of previous studies which demonstrated lower toxicity rate, with comparable efficacy outcomes with full-dose FOLFIRINOX.^{25,30,32} Our experience suggests that modest dose attenuations, in conjunction with the use of growth factor support as a secondary prophylaxis, are associated with less toxicity than observed in the FOLFIRINOX-

treated patients reported by Conroy et al.¹⁵ Although 22% of our patients had biliary stents for obstruction, we observed only three cases of cholangitis which recovered after antibiotic therapy. Chemotherapy remains the mainstay of treatment for patients with metastatic pancreatic cancer. The alternative sequence of the active drugs would be interesting as recently reported in metastatic pancreatic cancer.^{34,35} FOLFIRINOX and Gem/nab-*P* are both approved for the first-line treatment of this cancer; however, present different median OS (11.1 vs 8.5 months), PFS (6.6 vs 3.3 months), and objective RR (32% vs 33%) in favor of FOLFIRINOX, they present moreover different toxicities and Gem/Nab-*P* shows a better tolerance.^{15,20} It must be emphasized that the results of a Markov analytical decision model showed FOLFIRINOX to be cost-effective, especially with the reduced cost of using generic drugs, as performed in our series of patients in which generic drugs were used.³⁶

Conclusion

In conclusion, with the limitations of a retrospective study our results demonstrate that attenuated dose of FOLFIRINOX is feasible in outpatients with metastatic/advanced pancreatic cancer in a general hospital, in the real-world clinical practice, the dose reduction as performed in our patients did not compromise efficacy, but reduced the number of AE.

It must be emphasized, however, that a rising incidence of pancreatic cancer is projected to become the second leading cause of cancer-related deaths, so there is a great need to develop more effective therapies, and the management of this disease will require prioritizing clinical trial enrolment whenever possible, rather than prioritizing standard of care treatment.²⁹

Disclosure

LC declares consulting and advisory roles with Astrazeneca and Merck, and travel, accommodations and expenses from Pfizer, Ipsen, and Cellegene. The other authors report no conflicts of interest in this work.

References

1. Lambert A, Gavaille C, Conroy T. Current status on the place of FOLFIRINOX in metastatic pancreatic cancer and future directions. *Terap Adv Gastroenterol*. 2017;10(8):631–645. doi:10.1177/1756283X17713879
2. Siegel RL, Miller KD, Jemal A. Cancer statistics. *Cancer J Clin*. 2017;67:7–30. doi:10.3322/caac.21387
3. Sant M, Allemani C, Santaquilani M, Knijn A, Marchesi F, Capocaccia R, EURO CARE Working Group. EURO CARE-4. Survival of cancer patients diagnosed in 1995–1999. Results and commentary. *Eur J Cancer*. 2009;45:931–939. doi:10.1016/j.ejca.2008.11.018

4. Lefebvre AC, Maurel J, Bouteux S, et al. Pancreatic cancer: incidence, treatment and survival trends-1175 cases in Calvados (France) from 1978 to 20002. *Gastroenterol Clin Biol*. 2009;33:1045–1051. doi:10.1016/j.gcb.2009.04.011
5. Philip PA. Locally advanced pancreatic cancer: where should we go from here? *J Clin Oncol*. 2011;29:4066–4068. doi:10.1200/JCO.2011.37.2532
6. Burris HA, Moore MJ, Andersen J, et al. Improvement in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol*. 1997;15(6):2403–2413. doi:10.1200/JCO.1997.15.6.2403
7. Conroy T, Mitry E. Chimiothérapie de l'adénocarcinome du pancréas métastatique: défis et espoirs. *Bull Cancer*. 2011;98:1438–1446. doi:10.1684/bdc.2011.1494
8. Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson AB 3rd. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: eastern cooperative oncology group trial E2297. *J Clin Oncol*. 2002;20(15):3270–3275. doi:10.1200/JCO.2002.11.149
9. Herrmann R, Bodoky G, Ruhstaller T, et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multi center, phase III trial of the swiss group for clinical cancer research and the central European cooperative oncology group. *J Clin Oncol*. 2007;25(16):2212–2217. doi:10.1200/JCO.2006.09.0886
10. Louvet C, Labianca R, Hammel P, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol*. 2005;23(15):3509–3516. doi:10.1200/JCO.2005.06.023
11. Rocha Lima CM, Green MR, Rotche R, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increase tumor response rate. *J Clin Oncol*. 2004;22(18):3776–3783. doi:10.1200/JCO.2004.12.082
12. Kindler HL, Niedzwiecki D, Hollis D, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the cancer and leukemia group B (CALGB 80303). *J Clin Oncol*. 2010;28(22):3617–3622. doi:10.1200/JCO.2010.28.1386
13. Philip PA, Benedetti J, Corless CL, et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: southwest oncology group-directed intergroup trial S0205. *J Clin Oncol*. 2010;28(22):3605–3610. doi:10.1200/JCO.2009.25.7550
14. Moore MJ, Gldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada clinical trials group. *J Clin Oncol*. 2007;25(15):1960–1966. doi:10.1200/JCO.2006.07.9525
15. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817–1825. doi:10.1056/NEJMoa1011923
16. Chlilma MK, Cook N, Dhani NC, et al. FOLFIRINOX for advanced pancreatic cancer: the princess margaret cancer centre experience. *Br J Cancer*. 2016;115:649–654. doi:10.1038/bjc.2016.222
17. Di Valentin T, Biagi J, Bourque S, et al. Eastern canadian colorectal cancer consensus conference: standards of care for the treatment of patients with rectal, pancreatic, and gastrointestinal stromal tumours and pancreatic neuroendocrine tumours. *Curr Oncol*. 2013;20:e455–e464. doi:http://dx.doi.org/10.3747/co.20.1638
18. Moorcraft SY, Khan K, Peckitt C, et al. FOLFIRINOX for locally advanced or metastatic pancreatic ductal adenocarcinoma: the Royal Marsden experience. *Clin Colorectal Cancer*. 2014;13:232–238. doi:10.1016/j.clcc.2014.09.005
19. Rombousts SJ, Mungroop TH, Heilmann MN, et al. FOLFIRINOX in locally advanced and metastatic pancreatic cancer: a single centre cohort study. *J Cancer*. 2016;7:1861–1866. doi:10.7150/jca.16279
20. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369:1691–1703. doi:10.1056/NEJMoa1304369
21. Kim GP, Parisi MF, Patel BM, Pelletier CL, Belk KW. Comparison of treatment patterns, resource utilization, and cost of care in patients with metastatic pancreatic cancer treated with first-line nab-paclitaxel plus gemcitabine or FOLFIRINOX. *Expert Rev Clin Pharmacol*. 2017;10(5):559–565. doi:10.1080/17512433.2017.1302330
22. McBride A, Bonafede M, Cai Q, et al. Comparison of treatment patterns and economic outcomes among metastatic pancreatic cancer patients initiated on nab-paclitaxel plus gemcitabine versus FOLFIRINOX. *Expert Rev Clin Pharmacol*. 2017;1–8. doi:10.1080/17512433.2017.1365598
23. Rahman FAU, Ali S, Saif MW. Update on the role of nanoliposomal irinotecan in the treatment of metastatic pancreatic cancer. *Ther Adv Gastroenterol*. 2017;10(7):563–572.
24. Ducreux M, Seufferlein T, Van Laethem JL, et al. Systemic treatment of pancreatic cancer revisited. *Semin Oncol*. 2019;46(1):28–38.
25. Mahaseth H, Brucher E, Kauh J, et al. Modified FOLFIRINOX regimen with improved safety maintained efficacy in pancreatic adenocarcinoma. *Pancreas*. 2013;42:1311–1315. doi:10.1097/MPA.0b013e31829e2006
26. Lee JC, Kim JW, Ahn S, et al. Optimal dose reduction of FOLFIRINOX for preserving tumour response in advanced pancreatic cancer: using cumulative relative dose intensity. *Eur J Cancer*. 2017;76:125–133. doi:10.1016/j.ejca.2017.02.010
27. Li X, Mao T, Zhang Q, et al. Modified-FOLFIRINOX in metastatic pancreatic cancer: A prospective study in Chinese population. *Cancer Lett*. 2017;10(406):22–26. doi:10.1016/j.canlet.2017.07.012
28. Hashimoto M, Hikichi T, Suzuki T, et al. Successful chemotherapy with modified FOLFIRINOX for pancreatic acinar cell carcinoma. *Clin J Gastroenterol*. 2017;10(6):564–569. doi:10.1007/s12328-017-0785-5
29. Yoshida K, Iwashita T, Uemura S, et al. A multicenter prospective phase II study of first-line modified FOLFIRINOX for unresectable advanced pancreatic cancer. *Oncotarget*. 2017;8(67):111346–111355. doi:10.18632/oncotarget.22795
30. Ghorani E, Wong HH, Hewitt C, Calder J, Corrie P, Safety BB. Efficacy of modified FOLFIRINOX for advanced pancreatic adenocarcinoma: a UK single-centre experience. *Oncology*. 2015;89(5):281–287. doi:10.1159/000439171
31. Stein SM, James ES, Deng Y, et al. Final Analysis of phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer. *BJC*. 2016;114:737–743. doi:10.1038/bjc.2016.45
32. Gunturu KS, Yao X, Cong X, et al. FOLFIRINOX for locally advanced and metastatic pancreatic cancer: single institution retrospective review of efficacy and toxicity. *Med Oncol*. 2013;30(1):361. doi:10.1007/s12032-012-0361-2
33. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228–247. doi:10.1016/j.ejca.2008.10.026
34. Taieb J, Rinaldi Y, Pointet A-L, et al. Gemcitabine plus nab-paclitaxel until progression or given sequentially with 5-fluorouracil plus irinotecan (FOLFIRI.3) for first-line treatment of metastatic pancreatic ductal adenocarcinoma (mPDAC): a randomized phase II study (PRODIGE 37-FIRGEMAX). *J Clin Oncol*. 2018;36:4107. doi:10.1200/JCO.2018.36.15_suppl.4107
35. Assenat E, Fouchardiere CDL, Mollevi C, et al. Sequential treatment with Nab-paclitaxel plus gemcitabine and folfirinix in metastatic pancreatic adenocarcinoma: GABRINOX phase II results. *J Clin Oncol*. 2018;36(15 suppl):4109.
36. Tam VC, Ko YJ, Mittmann N, et al. Cost-effectiveness of systemic therapies for metastatic pancreatic cancer. *Curr Oncol*. 2013;20:90–106. doi:10.3747/co.20.1223

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Appendix COCKRUM01

Overall survival (OS) of patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with first-line (1L) FOLFIRINOX (FFX): Bridging the gap between the NAPOLI 3 trial and real-world practice.

Paul Cockrum, Rose Chang, Louise Huafeng Yu, Chunyi Xu, Mei Sheng Duh, George P. Kim; Ipsen Biopharmaceuticals, Inc., Crowley, TX; Analysis Group, Boston, MA; University of Florida/UF Health Cancer Center, Gainesville, FL

Background: NALIRIFOX (liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin) demonstrated significantly improved OS compared to 1L gemcitabine + nab-paclitaxel in the phase 3 NAPOLI 3 trial (NCT04083235). The median OS (95% CI) in the NALIRIFOX intention-to-treat population (N= 383) was 11.1 (10.0, 12.1) months. However, the relative efficacy of NALIRIFOX versus FFX (irinotecan + 5-fluorouracil/leucovorin + oxaliplatin), another standard of care for 1L treatment of mPDAC, has not been studied. To further contextualize findings from NAPOLI 3 trial, the current study described OS among patients treated with 1L FFX in the real-world setting. **Methods:** Three cohorts of patients with mPDAC treated with 1L FFX were identified from the Flatiron Health database. The all-comer cohort included all adult patients with mPDAC treated with 1L FFX since January 2014. Among them, the trial-aligned cohort included patients with mPDAC treated with 1L FFX between January 1, 2020 and July 31, 2022 (to align with the time period of NAPOLI 3 trial) who met the eligibility criteria of NAPOLI 3. Finally, a subgroup of patients in the trial-aligned cohort who received modified FFX (mFFX) regimen composed the trial-aligned mFFX cohort. OS was assessed using Kaplan-Meier analysis. **Results:** The all-comer cohort consisted of 3,271 patients. The trial-aligned cohort included 219 patients, of whom 154 (70%) were treated with mFFX. The distribution of baseline characteristics was similar across three cohorts (Table). The median age of the trial-aligned cohort was 65 years old, with 46% of patients being female, 67% being White, and 47% having ECOG score of 1. The median OS (95% CI) in the all-comer cohort and trial-aligned cohort was 9.0 (8.5, 9.3) months and 9.1 (7.8, 10.9) months, respectively; the median OS (95% CI) was 8.6 (7.3, 10.5) months in the trial-aligned mFFX cohort. **Conclusions:** NALIRIFOX regimen in the NAPOLI 3 trial showed numerically improved OS compared to FFX, including mFFX, in the real-world setting. Analysis adjusting for baseline characteristics are warranted and will provide further insights for the comparative efficacy of the two regimens. Research Sponsor: Ipsen Corp.

Characteristics of real-world FOLFIRINOX cohorts.

	All-comer cohort (N=3,271)	Trial-aligned cohort (N=219)	Trial-aligned mFFX cohort (N=154)
Baseline characteristics			
Age, years, mean (SD)	63.5 (9.0)	64.6 (8.2)	65.1 (8.5)
Female, n (%)	1,377 (42.1)	100 (45.7)	68 (44.2)
White, n (%)	2,118 (64.8)	146 (66.7)	100 (64.9)
ECOG score = 1, n (%)	1,327 (48.9)*	103 (47.0)	77 (50.0)
Endpoint			
Median OS, months (95% CI)	9.0 (8.5, 9.3)	9.1 (7.8, 10.9)	8.6 (7.3, 10.5)

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; SD, standard deviation.

*Proportion calculated based on 2,711 patients with ECOG available at baseline.

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Appendix CUI02

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A Chinese Retrospective Multicenter Study of First-Line Chemotherapy for Advanced Pancreatic Cancer

Authors' Contribution:

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Data Collection B

Statistical Analysis C

Data Interpretation D

Manuscript Preparation E

Literature Search F

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Background: Pancreatic cancer (PC) is a common digestive system tumor. For patients with advanced pancreatic cancer (APC), chemotherapy is still the predominant treatment. However, no large-scale clinical studies have been done of it as first-line therapy for APC. The goal of the present study was to assess real-world outcomes with chemotherapy in that setting.

Material/Methods: We retrospectively analyzed data from 322 patients with APC who were treated with chemotherapy at 4 hospitals in different cities in China. The first-line regimens used were AS (nab-paclitaxel and S-1), AG (nab-paclitaxel and gemcitabine), and FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin).

Results: Of the patients, 232 received AS, 79 received AG, and 11 received FOLFIRINOX. The median number of chemotherapy cycles was 5. The median overall survival (mOS) was 9 months and the median progression-free survival (mPFS) was 5 months. The AS, AG, and FOLFIRINOX regimens were associated with mOS rates of 9 months, 9 months, and 10 months, respectively. The mPFS rates for the AS, AG, and FOLFIRINOX regimens were 5, 4, and 5 months, respectively. The differences between the PFS rates for the regimens were statistically significant. The overall response rate (ORR) and overall disease control rate (DCR) for chemotherapy were 38% and 81.8%, respectively. The ORRs for the AS, AG, and FOLFIRINOX regimens were 46.9%, 18.7%, and 0%, respectively. The DCRs for the AS, AG and FOLFIRINOX regimens were 87.2%, 69.3%, and 63.6%, respectively. The differences between the ORRs and DCRs for the regimens were statistically significant. The incidences of grade 3/4 adverse events (AEs) associated with the AS, AG, and FOLFIRINOX regimens were 29.9%, 25%, and 36.4%, respectively.

Conclusions: The AS regimen was associated with a higher ORR and DCR than the other 2 regimens, with a lower rate of AEs.

MeSH Keywords: **Antineoplastic Agents • Drug-Related Side Effects and Adverse Reactions • Pancreatic Neoplasms**

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Background

Pancreatic cancer (PC) is an aggressive and lethal malignant solid tumor. The fourth most common cause of cancer-related death, it is associated with a 5-year survival rate of only 5%, even in patients who undergo curative surgery or are treated with chemotherapy and radiation therapy [1]. Estimates indicate that by 2030, PC will become the second leading cause of cancer death in the United States [2]. In 2018, it was estimated that there would be 458 918 new cases of cancer and 432 242 deaths from the disease worldwide [3]. Furthermore, for unknown reasons, the morbidity associated with PC is increasing globally. Pancreatic ductal adenocarcinoma is the most common type of PC, accounting for 90% of cases.

The incidence of PC is highest in East Asia, North America, and Eastern Europe. More than one-third of all new diagnoses occur in East Asia. In China, it is ranked ninth and sixth, respectively, in morbidity and mortality from PC. In 2018, 116 300 new cases and 110 400 deaths due to PC – or one-quarter of those in the world – occurred in China, making it the country most affected by the disease. Some patients with early-stage PC undergo radical surgery, but their survival rates are not very high, and most of them go on to experience recurrence or disease progression. Early detection of PC is hindered by a lack of visible symptoms and biomarkers [1,4], which is why more than 50% of patients with it are diagnosed at an advanced stage and have poor prognoses. Chemotherapy remains the optimal treatment for the majority of individuals who have advanced PC at diagnosis or whose disease relapses after surgery.

Unfortunately, few drugs have been shown to be effective against advanced PC (APC). In 2011, Conroy et al. demonstrated that in patients with metastatic PC, FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) was associated with a median overall survival (OS) of 11.1 months versus 6.8 months for gemcitabine, a statistically significant difference. Therefore, FOLFIRINOX became the standard first-line regimen for patients with APC [5]. However, no individuals older than age 75 years were included in the 2011 study. A single-center, retrospective analysis indicated that for patients with APC who are older than age 75 years, the use of modified FOLFIRINOX had efficacy similar to that in younger patients [6]. A phase 3 study by Von Hoff et al., published in 2013, demonstrated an improved OS of 8.5 months in patients given gemcitabine and nab-paclitaxel (AG), compared with 6.7 months for gemcitabine alone, establishing the AG regimen as another option for first-line chemotherapy [7]. In the phase 3 JASPAC01 and GEST trials, rates of chemotherapy-related adverse events (AEs), and especially hematologic toxicity, were lower in patients who received S-1 monotherapy than in those treated with gemcitabine alone [8,9]. Another phase 2 clinical trial

indicated that nab-paclitaxel plus S-1 (AS) produced an encouraging overall response rate (ORR) of 50% and was associated with manageable toxicities. The median progression-free survival (mPFS) and median OS (mOS) rates for AS were 5.6 months and 9.4 months, respectively [10].

No large-scale clinical study has been performed of first-line chemotherapy for APC. Therefore, there is an urgent need to explore real-world experience with chemotherapy in this clinical setting. In this retrospective, multicenter study, we evaluated the effects of the 3 predominant regimens – AS, AG, and FOLFIRINOX – on outcomes of patients with APC in China.

Material and Methods

Study design and patients

Included in the study were 322 patients who received first-line chemotherapy with AS, AG, or FOLFIRINOX for APC at the Chinese PLA General Hospital (162 cases), Beijing Cancer Hospital (84 cases), Cancer Hospital/Chinese Academy of Medical Sciences (29 cases), and Harbin Medical University Cancer Hospital (47 cases) between January 2013 and December 2018. The APC diagnoses were histologically or cytologically proven and all of the patients provided written informed consent. This retrospective analysis was approved by the Ethics Committees of the Chinese PLA General Hospital. The study was conducted in accord with the Declaration of Helsinki recommendations for research involving human subjects.

Treatment

Nab-paclitaxel (120 mg/m²) was administered intravenously (IV) on Days 1 and 8. S-1 (120, 100, or 80 mg/day for body surface areas ≥ 1.5 m², between 1.25 m² and 1.5 m², and <1.25 m², respectively) was administered orally twice daily every 3 weeks on Days 1 to 14. Patients received gemcitabine (1000 mg/m²) IV on Days 1 and 8 plus nab-paclitaxel (120 mg/m²) IV on Days 1 and 8 every 3 weeks. Administration of 5-FU (400 mg/m² and 2400 mg/m²) was by IV and continuous infusion, respectively. IV administration of leucovorin (400 mg/m²), irinotecan (140 mg/m²), and oxaliplatin (85 mg/m²) was IV on Day 1 every 2 weeks. In our study, routine blood tests were performed before treatment. Treatment was withdrawn or the dosages reduced depending on the degree of AEs experienced by patients. Of the patients who had previously undergone surgery, 15 received adjuvant therapy. Five patients received the gemcitabine plus S-1 (GS) regimen, 7 received gemcitabine alone, 2 received S-1 alone, and 1 received the AG regimen.

Assessments

All of the patients had measurable lesions. The efficacy of chemotherapy was assessed using the Response Evaluation Criteria in Solid Tumors. All AEs were assessed using the Common Terminology Criteria for Adverse Events, version 3.0. Computed tomography scanning or magnetic resonance imaging was performed every 6 weeks until disease progression.

Statistical analysis

The primary endpoints of the study were the OS and PFS rates. The secondary endpoints were the disease control rate (DCR), defined as the percentage of patients who achieved a complete response (CR), partial response (PR), or who had disease that was stable disease for at least 8 weeks; the objective response rate (ORR), defined as the percentage of patients who achieved a CR or PR; and the toxicity of chemotherapy. A Kaplan-Meier analysis was performed to estimate survival benefit. We also collected data on patient demographics. All of the statistics were analyzed using IBM SPSS Statistics software (version 22.0).

Results

Patient characteristics

We recruited 322 patients for the analysis. Table 1 lists patient baseline characteristics, including age; sex; Eastern Cooperative Oncology Group score; tumor location; differentiation; number of metastases; levels of carcinoembryonic antigen, cancer antigen 19-9, and cancer antigen 125; and previous exposure to surgery or radiation therapy. The median age at diagnosis was 58.5 years (range 36–79). Of the patients, 62.4% (201) were men. The majority of patients (72%; 232) received AS as their first-line chemotherapy. Of the remaining patients, 79 received AG and 11 received FOLFIRINOX.

Efficacy

The median number of chemotherapy cycles was 5 (range 2–23). As of December 1, 2019, the 1-year survival rate was 31%. The mOS rate was 9 months (95% confidence interval [CI]: 8.1 to 9.9) (Figure 1A). The mPFS rate was 5 months (95% CI: 4.6 to 5.4) (Figure 1B). The mOS rates for the AS, AG, and FOLFIRINOX regimens were 9 months (95% CI: 8.1–9.9), 9 months (95% CI: 7.0–11.0), and 10 months (95% CI: 5.3–14.7) respectively. The mPFS rates for the AS, AG, and FOLFIRINOX regimens were 5 months (95% CI: 4.4–5.6), 4 months (95% CI: 3.1–4.9), and 5 months (95% CI: 2.9–7.1) respectively. There was no statistically significant difference in OS rates among the 3 regimens ($P=0.928$) (Figure 2A), but there was among the PFS rates ($P=0.001$) (Figure 2B).

The ORR to first-line chemotherapy was 38%. The ORRs for AS, AG, and FOLFIRINOX of 46.9%, 18.7%, and 0%, respectively, were statistically significantly different ($P=0.000$). The overall DCR was 81.8%. The DCRs for the AS, AG, and FOLFIRINOX regimens of 87.2%, 69.3%, and 63.6%, respectively, were statistically significantly different ($P=0.001$). Table 2 lists the rates of response to treatment in the patients.

Safety and tolerability

Table 3 lists data on the toxicity of the chemotherapy regimens. The overall rate of grade 3/4 AEs was 28.9%, including myelosuppression (23.4%), nausea and vomiting (1.9%), diarrhea (2.3%), neurotoxicity (2.9%), liver dysfunction (0.6%), alopecia (0.6%), oral mucositis (1%), and rash (0.3%). The grade 3/4 AE rates for the AS, AG, and FOLFIRINOX regimens were 29.9%, 25%, and 36.4%, respectively. Intestinal obstruction occurred in 2 patients and pancreatitis occurred in 1 patient during treatment. In the majority of the patients, the AEs associated with chemotherapy were manageable and tolerable.

Discussion

In this retrospective, multicenter analysis, we included 322 patients with APC who received AS, AG, or FOLFIRINOX as their first-line chemotherapy. The ORRs for AS, AG, and FOLFIRINOX were 46.9%, 18.7%, and 0%, respectively, and their DCRs were 87.2%, 69.3%, and 63.6%, respectively. Given the statistically significant differences in the ORRs and the DCRs, we concluded that the AS regimen was more effective than the other 2 regimens, with the rate of grade 3/4 AEs at 29.9%, compared with 25% for AG and 36.4% for FOLFIRINOX. Although treatment-associated toxicities are unavoidable with chemotherapy, the regimens had distinctly different AE rates. Therefore, when selecting chemotherapy for APC, clinicians should assess the disease status of a patient and balance the benefits and risks of various treatments [11].

Nab-paclitaxel is a novel, albumin-bound, solvent-free, water-soluble formulation of paclitaxel. With it, in contrast to previous castor oil-based formulations, pre-medication to avoid hypersensitivity reactions is unnecessary [12]. In the GEST study, the curves for OS and PFS in the S-1 group were nearly identical to those in the gemcitabine group, confirming the non-inferiority of S-1 to gemcitabine in terms of those 2 outcomes. Therefore, S-1, which offers the convenience of oral administration, can be used as first-line therapy for APC [9]. In a single-arm, phase 2 trial of 32 patients with APC reported by Wen Zhang et al. in 2018, use of AS followed by S-1 maintenance therapy resulted in ORRs and DCRs in the intent-to-treat (ITT) population of 53.1% and 87.5%, respectively. The mPFS rate was 6.2 months (range 4.4–8), and the mOS rate

Table 1. Baseline characteristics of the 322 patients in the trial.

Characteristic	AS (n=232)		AG (n=79)		FOLFIRINOX (n=11)		Total (n=322)		P value
	No.	%	No.	%	No.	%	No.	%	
Sex									0.275
Male	140	60.3	52	65.8	9	81.8	201	62.4	
Female	92	39.7	27	34.2	2	18.2	121	37.6	
Median age (range)	59 (36–79)		59 (37–74)		56 (43–67)		58.5 (36–79)		
ECOG PS									0.062
0	160	69.0	42	53.2	6	54.5	208	64.6	
1	71	30.6	35	44.3	5	45.5	111	34.5	
2	1	0.4	2	2.5	0	0.0	3	0.9	
Tumor location									
Head	87	39.0	30	40.5	2	20.0	119	38.8	0.309
Body	37	16.6	10	13.5	1	10.0	48	15.6	0.574
Tail	48	21.5	19	25.7	3	30.0	70	22.8	0.852
Body+tail	47	21.1	15	20.3	4	40.0	66	21.5	0.49
	4	1.8	0	0.0	0	0.0	4	1.3	
Differentiation									0.58
Poor	82	58.6	28	54.9	2	28.6	112	56.6	
Moderate	56	40.0	22	43.1	5	71.4	83	41.9	
High	2	1.4	1	2.0	0	0.0	3	1.5	
Metastasis numbers									0.393
1	145	63.9	43	58.1	4	40.0	192	61.7	
2	43	18.9	18	24.3	4	40.0	65	20.9	
≥3	39	17.2	13	17.6	2	20.0	54	17.4	
Metastatic type									
Liver	160	69.0	53	67.1	5	45.5	218	67.7	0.263
Lung	21	9.1	7	8.9	2	18.2	30	9.3	0.588
Bone	13	5.6	6	7.6	0	0.0	19	5.9	0.567
Lymph node	119	51.3	35	44.3	5	45.5	159	49.4	0.543
Adrenal gland	10	4.3	2	2.5	1	9.1	13	4.0	0.54
Operation									0.376
Yes	50	21.6	23	29.1	3	27.3	76	23.6	
No	182	78.4	56	70.9	8	72.7	246	76.4	
CEA									0.143
Normal	87	40.0	39	52.7	4	36.4	130	42.9	
Abnormal	131	60.0	35	47.3	7	63.6	173	57.1	
CA 19-9									0.508
Normal	34	15.3	14	18.4	3	27.3	51	16.5	
Abnormal	188	84.7	62	81.6	8	72.7	258	83.5	
CA 125									0.312
Normal	44	23.2	14	27.5	4	44.4	62	24.8	
Abnormal	146	76.8	37	72.5	5	55.6	188	75.2	
Median chemotherapy cycles (range)	6 (2–23)		4 (2–12)		6 (3–16)		5 (2–23)		
Radiotherapy									0.79
Yes	44	19.0	15	19.0	3	27.3	62	19.3	
No	188	81.0	64	81.0	8	72.7	260	80.7	

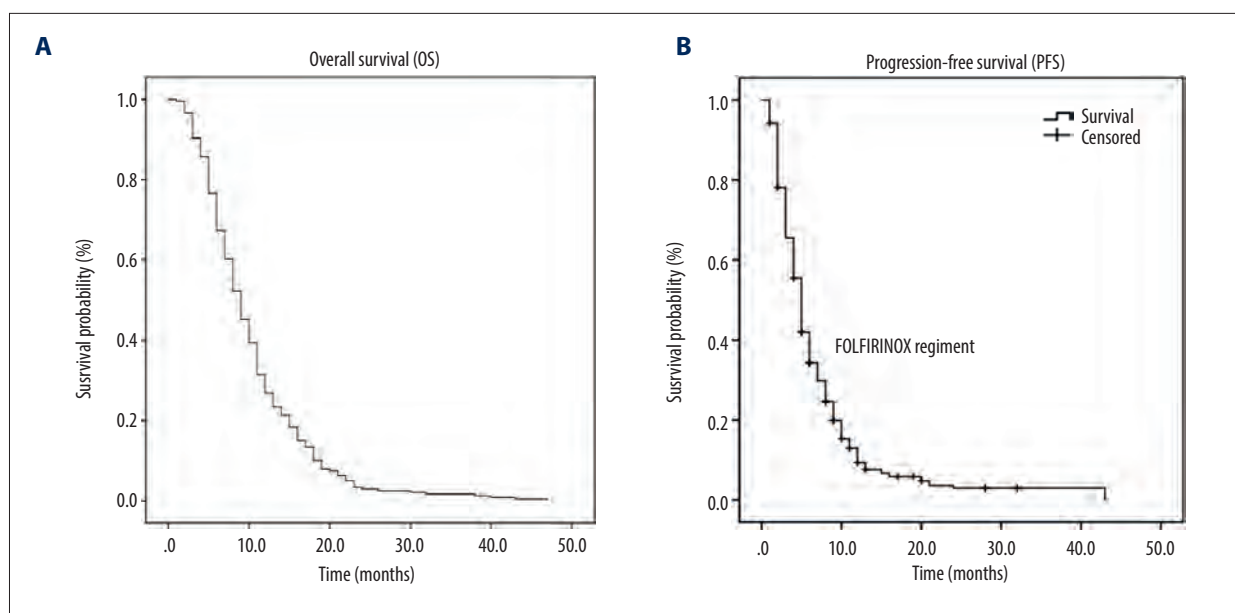


Figure 1. Kaplan-Meier curve of overall survival (OS) and progression-free survival (PFS) in all patients. (A) OS in all patients in the trial. (B) PFS in all patients in the trial.

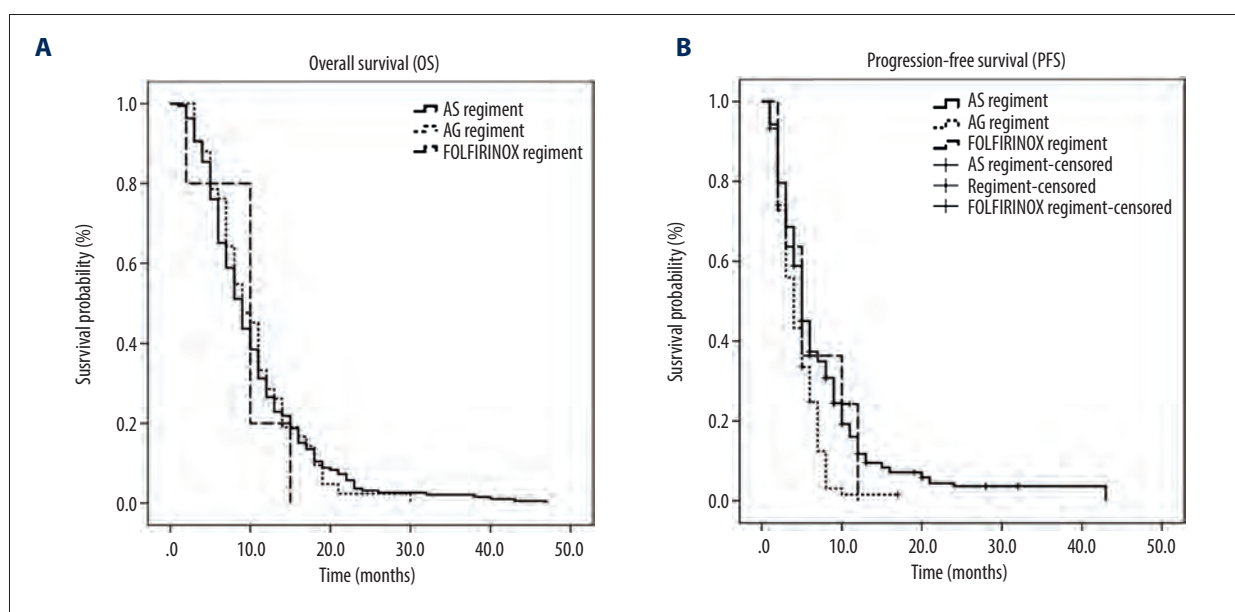


Figure 2. Kaplan-Meier curve of overall survival (OS) and progression-free survival (PFS) in patients treated with the regimens. (A) OS in patients treated with nab-paclitaxel and S-1 (AS), ab-paclitaxel and gemcitabine (AG), and 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX). (B) PFS of patients treated with the AS, AG, and FOLFIRINOX.

was 13.6 months (range 8.7–18.5). The incidence of grade 3/4 neutropenia was 27.6% [13], which was similar to our study. In another single-arm, single-center, phase 2 trial, AS and GS were administered to patients with APC. The mPFS and mOS rates were 5.6 months and 9.4 months, respectively, and the ORR was 50% in the ITT population [10]. The median times to progression (TTP) in the 2 groups were 7.1 months (95% CI: 4.5–9.7) and 3.6 months (95% CI: 1.8–5.4), respectively. The

mOS rates were 10.2 months (95% CI: 9.1–11.3) and 6 months (95% CI: 4.2–7.8), respectively, which indicates that AS was associated with a prolonged median TTP ($P=0.022$) and improved mOS ($P<0.001$) [14].

Gemcitabine-based combination regimens, with either S-1 or nab-paclitaxel, have been associated with more frequent chemotherapy-related AEs [15,16]. Previous clinical trials support

Table 2. Rates of treatment response in patients in the trial.

Event	AS		AG		FOLFIRINOX		P value	
	Any grade (%)	Grade 3/4(%)	Any grade (%)	Grade 3/4(%)	Any grade (%)	Grade 3/4 (%)	Any grade (%)	Grade 3/4 (%)
Myelosuppression	151 (68.3)	54 (24.4)	61 (63.2)	15 (19.7)	9 (81.8)	3 (27.3)	0.44	0.619
Neurotoxicity	97 (43.9)	7 (3.2)	15 (19.7)	2 (2.6)	2 (18.2)	0	0.006	
Diarrhea	26 (12.3)	5 (2.3)	10 (13.2)	0	4 (36.4)	2 (18.2)	0.002	
Nausea and vomiting	114 (51.6)	4 (1.8)	35 (46.1)	1 (1.3)	5 (45.5)	1 (9.1)	0.664	
Liver dysfunction	33 (14.9)	1 (0.5)	10 (13.2)	1 (1.3)	4 (36.4)	0	0.502	
Alopecia	50 (22.6)	2 (0.9)	2 (2.6)	0	0	0	0.005	
Oral mucositis	8 (3.6)	3 (1.4)	0	0	0	0	0.779	
Rash	11 (5)	1 (0.5)	1 (1.3)	0	0	0	0.832	
Total		66 (29.9)		19 (25)		4 (36.4)		

Table 3. Rates of adverse events in patients in the trial.

Variable	AS (n=211)		AG (n=75)		FOLFIRINOX (n=11)		Total (n=297)		P value
	No.	%	No.	%	No.	%	No.	%	
Response									
Complete response	2	0.9	0	0.0	0	0.0	2	0.7	
Partial response	97	46.0	14	18.7	0	0.0	111	37.3	
Stable disease	85	40.3	38	50.7	7	63.6	130	43.8	
Progressive disease	27	12.8	23	30.7	4	36.4	54	18.2	
Objective response rate	98	46.9	14	18.7	0	0.0	113	38.0	0.000
Disease control rate	184	87.2	52	69.3	7	63.6	243	81.8	0.001

the conclusion that FOLFIRINOX is more toxic than gemcitabine and nab-paclitaxel [17]. In Asia, most patients with APC cannot tolerate the AEs associated with FOLFIRINOX; therefore, its application is limited. Both FOLFIRINOX and gemcitabine/nab-paclitaxel can be offered to patients who have good performance status.

There were also some limitations to the present study. First, only 11 patients were treated with FOLFIRINOX, which may explain why the regimen was not very effective. Second, we did not collect enough data on genetic testing because it is not covered by medical insurance in China and is so expensive that most patients cannot afford it. Further study is needed of the relationship between the expression of certain genes and the prognosis for APC.

Conclusions

In conclusion, AS and AG are safe and effective alternative regimens for APC. Moreover, in the present study, AS was more effective than AG and the favorable response to it showed that it has promise in patients with APC. These results should be confirmed by additional prospective, randomized trials. Individualized precision therapy should be the treatment of choice for patients diagnosed with unresectable PC.

Conflicts of interest

None.

References:

1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2019. *Cancer J Clin*, 2019; 69(1): 7–34
2. Rahib L, Smith BD, Aizenberg R et al: projecting cancer incidence and deaths to 2030: The unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res*, 2014; 74(11): 2913–21
3. Bray F, Ferlay J, Soerjomataram I et al: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Cancer J Clin*, 2018; 68(6): 394–424
4. Adamska A, Domenichini A, Falasca M: Pancreatic ductal adenocarcinoma: Current and evolving therapies. *Int J Mol Sci*, 2017; 18(7): 1338
5. Conroy T, Desseigne F, Ychou M et al: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*, 2011; 364(19): 1817–25
6. Mizrahi JD, Rogers JE, Hess KR et al: Modified FOLFIRINOX in pancreatic cancer patients age 75 or older. *Pancreatol*, 2020; 20(3): 501–4
7. Von Hoff DD, Ervin T, Arena FP et al: Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*, 2013; 369(18): 1691–703
8. Maeda A, Boku N, Fukutomi A et al: Randomized phase III trial of adjuvant chemotherapy with gemcitabine versus S-1 in patients with resected pancreatic cancer: Japan Adjuvant Study Group of Pancreatic Cancer (JASPAC-01). *Jpn J Clin Oncol*, 2008; 38(3): 227–29
9. Ueno H, Ioka T, Ikeda M et al: Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. *J Clin Oncol*, 2013; 31(13): 1640–48
10. Shi Y, Zhang S, Han Q et al: Nab-paclitaxel plus S-1 in advanced pancreatic adenocarcinoma (NPSPAC): A single arm, single center, phase II trial. *Oncotarget*, 2017; 8(54): 92401–10
11. Chen J, Chen L, Yu J et al: Meta-analysis of current chemotherapy regimens in advanced pancreatic cancer to prolong survival and reduce treatment-associated toxicities. *Mol Med Rep*, 2019; 19(1): 477–89
12. Neesse A, Michl P, Tuveson DA, Ellenrieder V: Nab-Paclitaxel: Novel clinical and experimental evidence in pancreatic cancer. *Z Gastroenterol*, 2014; 52(4): 360–66
13. Zhang W, Du C, Sun Y et al: Nab-paclitaxel plus S-1 as first-line followed by S-1 maintenance for advanced pancreatic adenocarcinoma: A single-arm phase II trial. *Cancer Chemother Pharmacol*, 2018; 82(4): 655–60
14. Xu Y, Guo X, Fan Y et al: Efficacy and safety comparison of nabpaclitaxel plus S-1 and gemcitabine plus S-1 as first-line chemotherapy for metastatic pancreatic cancer. *Jpn J Clin Oncol*, 2018; 48(6): 535–41
15. Von Hoff DD, Ervin T, Arena FP et al: Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*, 2013; 369(18): 1691–703
16. Sudo K, Takeshi I, Hirata N et al: Randomized controlled study of gemcitabine plus S-1 combination chemotherapy versus gemcitabine for unresectable pancreatic cancer. *Cancer Chemother Pharmacol*, 2014; 73(2): 389–96
17. Muranaka T, Kuwatani M, Komatsu Y et al: Comparison of efficacy and toxicity of FOLFIRINOX and gemcitabine with nab-paclitaxel in unresectable pancreatic cancer. *J Gastrointest Oncol*, 2017; 8(3): 566–71

Appendix CV

June A. Munford
Curriculum Vitae

Education

University of Wisconsin-Milwaukee - MS, Library & Information Science, 2009
Milwaukee, WI

- Coursework included cataloging, metadata, data analysis, library systems, management strategies and collection development.
- Specialized in library advocacy, cataloging and public administration.

Grand Valley State University - BA, English Language & Literature, 2008
Allendale, MI

- Coursework included linguistics, documentation and literary analysis.
- Minor in political science with a focus in local-level economics and government.

Professional Experience

Researcher / Expert Witness, October 2017 – present
Freelance ● Pittsburgh, Pennsylvania & Grand Rapids, Michigan

- Material authentication and public accessibility determination. Declarations of authenticity and/or public accessibility provided upon research completion. Experienced with appeals and deposition process.
- Research provided on topics of public library operations, material publication history, digital database services and legacy web resources.
- Past clients include Alston & Bird, Arnold & Porter, Baker Botts, Fish & Richardson, Erise IP, Irell & Manella, O'Melveny & Myers, Perkins-Coie, Pillsbury Winthrop Shaw Pittman and Slayden Grubert Beard.

Library Director, February 2013 - March 2015
Dowagiac District Library ● Dowagiac, Michigan

- Executive administrator of the Dowagiac District Library. Located in Southwest Michigan, this library has a service area of 13,000, an annual operating budget of over \$400,000 and total assets of approximately \$1,300,000.

- Developed careful budgeting guidelines to produce a 15% surplus during the 2013-2014 & 2014-2015 fiscal years while being audited.
- Using this budget surplus, oversaw significant library investments including the purchase of property for a future building site, demolition of existing buildings and building renovation projects on the current facility.
- Led the organization and digitization of the library's archival records.
- Served as the public representative for the library, developing business relationships with local school, museum and tribal government entities.
- Developed an objective-based analysis system for measuring library services - including a full collection analysis of the library's 50,000+ circulating items and their records.

November 2010 - January 2013

Librarian & Branch Manager, Anchorage Public Library ● Anchorage, Alaska

- Headed the 2013 Anchorage Reads community reading campaign including event planning, staging public performances and creating marketing materials for mass distribution.
- Co-led the social media department of the library's marketing team, drafting social media guidelines, creating original content and instituting long-term planning via content calendars.
- Developed business relationships with The Boys & Girls Club, Anchorage School District and the US Army to establish summer reading programs for children.

June 2004 - September 2005, September 2006 - October 2013

Library Assistant, Hart Area Public Library

Hart, MI

- Responsible for verifying imported MARC records and original MARC cataloging for the local-level collection as well as the Michigan Electronic Library.
- Handled OCLC Worldcat interlibrary loan requests & fulfillment via ongoing communication with lending libraries.

Professional Involvement

Alaska Library Association - Anchorage Chapter

- Treasurer, 2012

Library Of Michigan

- Level VII Certification, 2008
- Level II Certification, 2013

Michigan Library Association Annual Conference 2014

- New Directors Conference Panel Member

Southwest Michigan Library Cooperative

- Represented the Dowagiac District Library, 2013-2015

Professional Development

Library Of Michigan Beginning Workshop, May 2008

Petoskey, MI

- Received training in cataloging, local history, collection management, children's literacy and reference service.

Public Library Association Intensive Library Management Training, October 2011

Nashville, TN

- Attended a five-day workshop focused on strategic planning, staff management, statistical analysis, collections and cataloging theory.

Alaska Library Association Annual Conference 2012 - Fairbanks, February 2012

Fairbanks, AK

- Attended seminars on EBSCO advanced search methods, budgeting, cataloging, database usage and marketing.

Depositions

2019 • Fish & Richardson

Apple v. Qualcomm (Case No. IPR2018-001281, 39521-00421IP, IPR2018-01282 and 39521-00421IP2)

2019 • Erise IP

Implicit, LLC v. Netscout Systems, Inc (Case No. 2:18-cv-53-JRG)

2019 • Perkins-Coie

Adobe Inc. v. RAH Color Technologies LLC (Case No. IPR2019-00627, IPR2019-00628, IPR2019-00629 and IPR2019-00646)

2020 ● O'Melveny & Myers

Maxell, Ltd. v. Apple Inc. (Case No. 5:19-cv-00036-RWS)

2021 ● Pillsbury Winthrop Shaw Pittman LLP

Intel v. SRC (Case No. IPR2020-1449)

2022 ● Perkins-Coie

Realtek v. Future Link (Case No. IPR2021-01182)

2023 ● Fish & Richardson

Neuroderm Ltd. v. Abbvie, Inc (Case No. PGR2022-00040)

2023 ● Fish & Richardson

Nearmap US Inc. v. Pictometry International Corp. (Case No. IPR2022-00735)

2023 ● Fish & Richardson

Samsung Electronics v. MemoryWeb LLC (Case No. 39843-0136PS1)

2023 ● Pillsbury Winthrop Shaw Whitman LLP

Gravel Rating Systems v. Costco Wholesale Corp. (Case No. 4:21-cv-149-ALM)

2024 ● Willkie-Farr

Netflix, Inc. v. VideoLabs. Inc. (Case No. IPR2023-00628)

2024 ● Quinn Emanuel Urquhart & Sullivan

Purdue University v. Wolfsped (Case No. 1:21-CV-840)

2024 ● Fish & Richardson

Dish Network v. Entropic Communications (Case No. IPR2024-00393)

2025 ● Perkins Coie

Amazon.com, Inc. v. Nokia Technologies Oy (Case No. IPR2024-00572)

2025 ● Fish & Richardson

Dish Network v. Entropic Communications (Case No. IPR2024-00373)

Limited Case and Clientele History

Alston & Bird

- Ericsson

v. Collision Communications (Case No. IPR2022-01233)

- Nokia

v. Neptune Subsea, Xtera (Case No. 1:17-cv-01876)

- Universal Electronics Inc

v. Roku Inc (Case No. IPR2022-00818)

Alavi & Anaipakos PLLC

- Stingray Group Inc. and Stingray Music USA, Inc.

v. Edwin A. Hernandez-Mondragon and Eglia Corp. (Case No. 1:24-cv-21226-RAR)

Arnold & Porter

- Ivantis

v. Glaukos (Case No. 8:18-cv-00620)

- Samsung

v. Jawbone (Case No. 2:21-cv-00186)

Benesch Friedlander Coplan & Aronoff

- Voyis
v. Cathx (Case No. 5:21-cv-00077-RWS)

Buchanan, Ingersoll & Rooney PC

- Google LLC, AT&T Service Inc., T Mobile USA Inc., Cellco Partnership, Ericsson Inc. & Nokia of America Corp.
v. KT Corp & Pegasus Wireless Innovation LLC (Case No. IPR2025-00293)

Deschert LLP

- Smaxtec Animal Care
v. ST Reproductive Technologies, LLC (Case No. IPR2024-00885)

Duane Morris

- Kangxi Communication Technologies
v. Skyworks Solutions Inc. (Case No. IPR2025-00373)
- Microsoft
v. Edge Networking Systems LLC (Case No. 1:24-cv-00215)

Erise I.P.

- Apple
v. Ericsson Inc. (Case No. IPR2022-00715)
v. Future Link Systems (Case No. IPRs 6317804, 6622108, 6807505, and 7917680)
v. INVT (Case No. 20-1881)
v. Navblazer LLC (Case No. IPR2020-01253)
v. Qualcomm (Case No. IPR2018-001281, 39521-00421IP, IPR2018-01282, 39521-00421IP2)

- v. Quest Nettech Corp (Case No. 2:19-cv-00118-JRG)
- v. Telefonaktiebolaget LM Ericsson (Case No. IPR2022-00275)
- v. Theta IP, LLC (Case No. IPR2024-00818)
- v. THL Holding Company LLC (Case No. 1:23-cv-00548)

- Fanduel

- v. CGT (Case No. 19-1393)

- Garmin

- v. Phillips North America LLC (Case No. 2:19-cv-6301-AB-KS)

- Netscout

- v. Longhorn HD LLC (Case No. 2:20-cv-00349)
 - v. Implicit, LLC (Case No. 2:18-cv-53-JRG)

- Sony Interactive Entertainment LLC

- v. Bot M8 LLC (Case No. IPR2020-01288)
 - v. Infernal Technology LLC (Case No. 2:19-CV-00248-JRG)

- Tesla

- v. Charge Fusion Technologies LLC (Case No. IPR2025-00032)

- Unified Patents

- v. GE Video Compression (Case No. 2:19-cv-248)

Fish & Richardson

- Apple

- v. AliveCor (Case No. 3:21-cv-03958)
 - v. LBS Innovations (Case No. 2:19-cv-00119-JRG-RSP)
 - v. Koss Corporation (Case No. IPR2021-00305)

- v. Masimo (Case No. IPR 50095-0012IP1, 50095-0012IP2, 50095-0013IP1, 50095-0013IP2, 50095-0006IP1, 50095-0135IP1)
- v. Neonode (Case No. 21-cv-08872-EMC)
- v. Qualcomm (Case No. IPR2018-001281, 39521-00421IP, IPR2018-01282, 39521-00421IP2)
- v. Resonant Sys. (Case No. 7:23-cv-00077-ADA)
- AsusTek Computer Inc.
 - v. Videolabs, Inc. (Case No. 22-CV-00720-ADA)
- Dell
 - v. Neo Wireless (Case No. IPR2022-00616)
- Dish Network
 - v. Entropic Communications, LLC (Case No. 2:2023-CV-01043)
 - v. Entropic Communications LLC (Case No. IPR2024-00393)
 - v. Realtime Adaptive Streaming (Case No. 1:17-CV-02097-RBJ)
 - v. TQ Delta LLC (Case No. 18-1798)
- Evapco Dry Cooling
 - v. SPG Dry Cooling (Case No. IPR2021-00688)
- Genetec
 - v. Sensormatic Electronics (Case No. 1:20-CV-00760)
- Huawei
 - v. Bell Northern Research LLC (Case No. IPR2019-01174)
- Kianxis
 - v. Blue Yonder (Case No. 3:20-cv-03636)

- LG Electronics
 - v. Bell Northern Research LLC (Case No. 3:18-cv-2864-CAB-BLM)
- MediaTek
 - v. MOSAID (Case No. IPR2024-00718)
- Metaswitch
 - v. Sonus Networks (Case No. IPR2018-01719)
- Microsoft
 - v. Throughputer Inc (Case No. IPR2022-00757)
- Mom Enterprises
 - v. Ddrops Company (Case No. 1:22-cv-00332)
- MLC Intellectual Property
 - v. MicronTech (Case No. 3:14-cv-03657-SI)
- Nearmap Inc
 - v. EagleView Technologies (Case No. IPR2022-01009)
- Neuroderm Ltd.
 - v. Abbvie, Inc (Case No. PGR2022-00040)
- Posco Co Ltd.
 - v. Pascal Drillet et al. (Case No. IPR2025-00370)
- Realtek Semiconductor
 - v. Future Link (Case No. IPR2021-01182)

- Quectel
 - v. Koninklijke Philips (Case No. 1:20-cv-01710)
- Samsung
 - v. Aire Technology (Case No. IPR2022-00877)
 - v. Bell Northern Research (Case No. 2:19-cv-00286-JRG)
 - v. Communication Technologies Inc (Case No. IPR2022-01221)
 - v. Jawbone Innovations (Case No. IPR2022-00865)
 - v. MemoryWeb LLC (Case No. IPR2022-00885)
 - v. Dodots Licensing Solutions (Case No. IPR2023-00701)
 - v. Telefonaktiebolaget LM Ericsson (Case No. IPR2021-00615)
- Texas Instruments
 - v. Vantage Micro LLC (Case No. IPR2020-01261)
- Xilinx
 - v. Sentient Sensors LCC (Case No. 1:22-cv-00173)

Goodwin Proctor

- Intel
 - v. Proxense, LLC (Case No. 6:24-cv-00283)
- Samsung Electronics
 - v. Mobile Data Technologies (Case No. 2:24-cv-00435)
- Taiwan Semiconductor Manufacturing Company Ltd.
 - v. Advanced Integrated Circuit Process LLC (Case No. 2:24-cv-00623)

Groombridge Wu

- Nearmap

v. Eagle View Technologies Inc. and Pictometry International Corp. (Case No. 2:21-cv-00283-TS-DAO)

Irell & Manella

- Curium

Latham & Watkins LLP

- Apple

v. Advanced Coding Research LLC

Leydig, Voit & Mayer, Ltd.

- Public Availability Consultancy

O'Melveny & Myers

- Apple

v. Maxell (Case No. 5:19-cv-00036-RWS)

- Disney Media & Entertainment Distribution LLC

v. Digital Media Technology Holdings, LLC (Case No. 2:22-cv-01642)

- Micron Technology Inc.

v. Besang Inc (Case No. IPR2023-00900)

- Samsung

v. Daedalus Prime LLC (1335 Investigation)

Perkins-Coie

- Amazon
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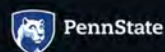
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Appendix DELACRUZ02

Diagnosis and Management of Pancreatic Cancer

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Pancreatic cancer remains the fourth leading cause of cancer-related deaths in the United States. Risk factors include family history, smoking, chronic pancreatitis, obesity, diabetes mellitus, heavy alcohol use, and possible dietary factors. Because more than two-thirds of adenocarcinomas occur in the head of the pancreas, abdominal pain, jaundice, pruritus, dark urine, and acholic stools may be presenting symptoms. In symptomatic patients, the serum tumor marker cancer antigen 19-9 can be used to confirm the diagnosis and to predict prognosis and recurrence after resection. Pancreas protocol computed tomography is considered standard for the diagnosis and staging of pancreatic cancer. Although surgical resection is the only potentially curative treatment for pancreatic ductal adenocarcinomas, less than 20% of surgical candidates survive five years. The decision on resectability requires multidisciplinary consultation. Pancreatic resections should be performed at institutions that complete at least 15 of the surgeries annually. Postoperatively, use of gemcitabine or fluorouracil/leucovorin as adjuvant chemotherapy improves overall survival by several months. However, more than 80% of patients present with disease that is not surgically resectable. For patients with locally advanced or metastatic disease, chemoradiotherapy with gemcitabine or irinotecan provides clinical benefit and modest survival improvement. Palliation should address pain control, biliary and gastric outlet obstruction, malnutrition, thromboembolic disease, and depression. (*Am Fam Physician*. 2014;89(8):626-632. Copyright © 2014 American Academy of Family Physicians.)

CME This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz Questions on page 623.

Author disclosure: No relevant financial affiliations.

► **Patient information:** A handout on this topic, written by the authors of this article, is available at <http://www.aafp.org/afp/2014/0415/p626-s1.html>. Access to the handout is free and unrestricted.

The American Cancer Society estimated 43,920 cases of pancreatic cancer, with approximately 37,390 deaths, in the United States in 2012. It remains the fourth leading cause of cancer-related deaths.¹ The age-adjusted annual incidence rates of pancreatic cancer in men and women have been slowly increasing, but it remains an uncommon cancer. Although there is an equal prevalence in both sexes, there is a slightly higher occurrence in black persons compared with white persons.² More than 90% of these cancers are pancreatic ductal adenocarcinomas, which are the focus of this review.³

Risk Factors

There are several risk factors associated with the development of pancreatic ductal adenocarcinoma³⁻⁵ (Table 1⁶). Although the risk from smoking is relatively low compared with other risks, based on the current smoking prevalence rates, 25% to 30% of all pancreatic cancer is attributable to tobacco exposure. In familial pancreatic cancer, two or more first-degree relatives have

pancreatic cancer in the absence of other cancer syndromes or other known genetic defects. In contrast, the very high-risk genetic and familial syndromes are rare, ranging from one in 280,000 persons for Peutz-Jeghers syndrome to 1% of the Ashkenazi Jewish population for *BRCA1* and *BRCA2*. Therefore, these syndromes account for 10% or less of pancreatic cancers.⁴

Screening and Primary Prevention

The U.S. Preventive Services Task Force recommends against routine screening for pancreatic cancer in asymptomatic adults who are at average risk because of lack of mortality benefit.⁷ However, it may be reasonable to consider screening persons at high risk of developing pancreatic ductal adenocarcinomas, such as persons from families with known genetic defects predisposing them to pancreatic cancer or with familial pancreatic cancer. Expert opinion recommends screening and surveillance with computed tomography (CT) or endoscopic ultrasonography.⁸

Diagnosis

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of suspected pancreatic cancer is broad given the wide range of nonspecific symptoms. Possibilities include, but are not limited to, cholangitis, cholecystitis, cholelithiasis, choledocholithiasis, choledochal cysts, duodenal or gastric ulcers, gastritis, pancreatitis, abdominal aortic aneurysm, lymphomas, and primary or secondary cancers of the biliary tree, liver, pancreas, stomach, or intestine.

CLINICAL EXAMINATION

Initial presenting symptoms may vary according to tumor location⁹ (Table 2¹⁰). More than 90% of these cancers are ductal adenocarcinomas, with more than two-thirds occurring in the head of the pancreas.³ Abdominal pain, jaundice, pruritus, dark urine, and acholic stools may be presenting symptoms as a result of obstruction within the biliary tree.¹¹ Nonspecific findings from cancers of the pancreatic body or tail include unexplained weight loss, anorexia, early satiety, dyspepsia, nausea, and depression.⁹ Also, a sudden onset of atypical type 2 diabetes mellitus that is difficult to control in a thin patient 50 years or older suggests pancreatic cancer.¹²

Physical examination findings for pancreatic cancer are also variable. Patients may present in early stages with normal examination findings or in advanced stages with manifestations of liver involvement such as abdominal tenderness, jaundice, and cachexia. A nontender, distended, palpable gallbladder in a patient with jaundice (Courvoisier sign) is 83% to 90% specific, but is only 26% to 55% sensitive for a biliary obstruction from malignancy.¹¹ Advanced pancreatic cancer, like other abdominal malignancies, can be associated with recurring superficial thrombophlebitis (Trousseau sign) or left supraclavicular lymphadenopathy (Virchow node). Subcutaneous areas of nodular fat necrosis (pancreatic panniculitis) may be evident in rare cases.¹³

DIAGNOSTIC TESTS

For many patients presenting with the common symptoms of pancreatic cancer, abdominal ultrasonography is a reasonable first imaging test. However, if ultrasonography is not diagnostic or pancreatic cancer is highly suggested by findings on the clinical examination, then

Table 1. Risk Factors for Pancreatic Cancer

Low increase (less than fivefold increase in risk)	Moderate increase (five- to 10-fold increase in risk)
Alcohol use (≥ four drinks per day)	BRCA2 gene carrier
Body mass index (≥ 30 kg per m ²)	Chronic pancreatitis
BRCA1 gene carrier	Cystic fibrosis
Chlorinated hydrocarbon exposure	Family history of pancreatic cancer in two first-degree relatives
Diabetes mellitus (type 2 for ≥ five years)	High increase (more than a 10-fold increase in risk)
Familial adenomatous polyposis	Familial atypical multiple mole melanoma
Family history of pancreatic cancer in one first-degree relative	Family history of pancreatic cancer in at least three first-, second-, or third-degree relatives
Hereditary nonpolyposis colorectal cancer	Hereditary pancreatitis
Polycyclic aromatic hydrocarbon exposure	Peutz-Jeghers syndrome
Tobacco use	

Adapted with permission from BMJ Publishing Group Limited. Brand RE, Lerch MM, Rubinstein WS, et al.; Participants of the Fourth International Symposium of Inherited Diseases of the Pancreas. *Advances in counseling and surveillance of patients at risk for pancreatic cancer.* Gut. 2007;56(10):1461.

Table 2. Prevalence of Pancreatic Cancer Symptoms

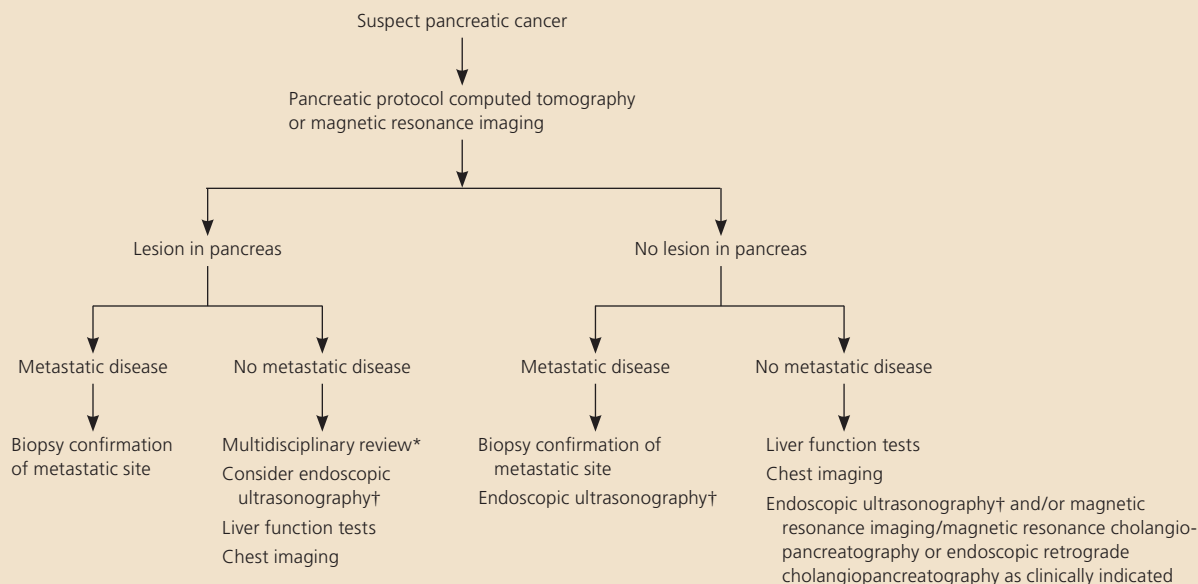
Symptoms	Patients (%)	Symptoms	Patients (%)
Cancer in the head of the pancreas		Cancer in the body and tail of the pancreas	
Weight loss	92	Unexplained weight loss	100
Jaundice	82	Pain	87
Abdominal pain	72	Nausea	43
Anorexia	64	Weakness	42
Dark urine	63	Vomiting	37
Acholic stool	62	Anorexia	33
Nausea	45	Constipation	27
Vomiting	37	Food intolerance	7
Weakness	35	Jaundice	7

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pancreas protocol CT is the standard for diagnosis and staging.^{14,15} Pancreas protocol CT involves triphasic (i.e., arterial, late, and venous phases) cross-sectional imaging that allows for enhancement between the parenchyma and adenocarcinoma.

If CT is not possible because of lack of availability or allergy to contrast media, magnetic resonance imaging with contrast media can be used to diagnose and stage pancreatic cancer. Magnetic resonance imaging, as well as magnetic resonance cholangiopancreatography, can be performed as an adjunct to CT in detecting extrapancreatic disease.³

Diagnosis of Suspected Pancreatic Cancer



*—Multidisciplinary review should ideally involve expertise from diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, surgery, and pathology.

†—Endoscopic ultrasonography-guided fine-needle aspiration if clinically indicated.

Figure 1. Diagnostic algorithm for suspected pancreatic cancer.

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If a pancreatic mass is identified, subsequent endoscopic ultrasonography and fine-needle aspiration are indicated. Pancreatic cysts identified on imaging also require endoscopic ultrasonography and fine-needle aspiration. Concerning cystic lesions of the pancreas include serous cystadenoma, mucinous cystic neoplasm, cyst-like dilations of the pancreatic duct such as intraductal papillary mucinous neoplasm, cystic degenerations or necrosis, cystic endocrine tumor, and ductal adenocarcinoma.¹⁶ If no mass is identified on cross-sectional imaging and no evidence of metastatic disease is present, further endoscopic ultrasonography, endoscopic retrograde cholangiopancreatography, magnetic resonance imaging, or magnetic resonance cholangiopancreatography is indicated.³

The most common serum tumor marker used for pancreatic ductal adenocarcinomas is cancer antigen 19-9, which is expressed in pancreatic and hepatobiliary disease. In symptomatic patients, it can help confirm the diagnosis and predict prognosis and recurrence after resection.³ However, cancer antigen 19-9 is not tumor-specific; therefore, it is not a sufficient individual screening tool for asymptomatic patients. Cancer antigen 19-9 has a limited sensitivity of 50% to 75% and

specificity of 80% to 85%; it cannot distinguish between cancer and chronic pancreatitis and possibly other disease states with chronic inflammation.¹⁷

A diagnostic algorithm for patients with suspected pancreatic cancer is provided in *Figure 1*.³

Staging

Detection of pancreatic cancer at an early stage is critical to curative treatment. Once a mass is identified and fine-needle aspiration confirms the diagnosis, endoscopic ultrasonography can determine tumor size and extent of lymph node metastases, and assess for portal venous system involvement to complete staging.³ In addition to endoscopic ultrasonography, chest CT and serum liver enzyme tests are useful to determine if a patient is a candidate for surgery.³ Diagnostic staging laparoscopy can be considered for detection of occult peritoneal metastases. *Table 3* lists the American Joint Committee on Cancer staging classification for pancreatic tumors, with data on pancreatic cancer distribution by stage and survival.^{18,19} A multidisciplinary team with expertise in surgery, diagnostic imaging, pathology, interventional endoscopy, and medical and radiation oncology is highly recommended to determine which patients are candidates for surgery.³

Treatment

RESECTABLE LESIONS

Surgical resection is the only potentially curative treatment for pancreatic ductal adenocarcinomas. Approximately 15% to 20% of patients have resectable disease, but less than 20% of patients who undergo surgery survive five years.³ The decision on resectability requires a multidisciplinary consultation, and distinction should be made between tumors that are resectable, borderline resectable, or unresectable (locally advanced and metastatic).²⁰ An expert consensus group has developed criteria to define tumor resectability, thereby identifying patients who will benefit from surgery (*Table 4*).^{3,21}

Although immediate postoperative mortality is less than 5%, the median survival is about 12 to 19 months.³ Studies support the recommendation that pancreatic resections should be performed at high-volume institutions, generally those that complete at least 15 pancreatic resections annually.²²⁻²⁶ Higher-volume centers have reported decreased mortality rates, shorter hospital stay, and lower overall cost compared with low-volume institutions.³

The classic surgery for resection of a carcinoma of the head of the pancreas is a pancreaticoduodenectomy, also known as a Whipple procedure. In this surgery, the gallbladder, common bile duct, second portion of the duodenum, and the head of the pancreas are resected with the postpyloric duodenum (pylorus-preserving pancreaticoduodenectomy), or the resection is continued proximally to include the distal stomach (classic pancreaticoduodenectomy). No differences in morbidity, mortality, or survival between the two procedures have been found.²⁷

Tumors involving the body or tail of the pancreas are rarely resectable. They are usually advanced at diagnosis and cause symptoms late in their development. For resectable lesions, the surgery performed is typically a distal pancreatectomy with or without splenectomy. Negative margin status, tumor DNA content, tumor size, and absence of lymph node metastasis are the strongest prognostic indicators for long-term survival.³

There is no standard for providing adjuvant treatment of pancreatic ductal adenocarcinomas postoperatively. Adjuvant

chemotherapy with gemcitabine (Gemzar) or fluorouracil/leucovorin improves survival by two to three months compared with observation alone, which can also be combined with gemcitabine- or fluoropyrimidine-based chemoradiation.^{3,28-30}

UNRESECTABLE LESIONS

More than 80% of patients present with disease that is not surgically resectable. Although a histologic diagnosis is not necessary before surgery, it is required for treatment of locally advanced, unresectable, or metastatic disease. Some studies have addressed the use of chemoradiation with or without chemotherapy to convert unresectable

Table 3. Tumor, Node, Metastasis Staging Classification for Pancreatic Cancer

Stage	Classifications	Clinical classification	Stage distribution at diagnosis* (%)	Five-year relative survival (%)
0	Tis, N0, M0	Localized within pancreas, resectable	8	21.5
IA	T1, N0, M0	Localized within pancreas, resectable		14
IB	T2, N0, M0	Localized within pancreas, resectable		12
IIA	T3, N0, M0	Locally invasive, resectable	27	7
IIB	T1, N1, M0 T2, N1, M0 T3, N1, M0	Locally invasive, resectable		5
III	T4, any N, M0	Locally advanced, unresectable		3
IV	Any T, any N, M1	Metastatic	53	1.9

Tumor: TX = primary tumor cannot be assessed; T0 = no evidence of primary tumor; Tis = carcinoma in situ; T1 = tumor limited to the pancreas, 2 cm or less in greatest dimension; T2 = tumor limited to the pancreas, more than 2 cm in greatest dimension; T3 = tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery; T4 = tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor).

Regional lymph nodes: NX = regional lymph nodes cannot be assessed; N0 = no regional lymph node metastasis; N1 = regional lymph node metastasis.

Distant metastasis: M0 = no distant metastasis; M1 = distant metastasis.

**—12% are unstaged at time of diagnosis.*

Adapted with permission from Edge SB, American Joint Committee on Cancer. AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer; 2010:293-294, with additional information from reference 19.

Table 4. Criteria for Determining Pancreatic Tumor Resectability

Localized and resectable	Unresectable
No distant metastases	Head
No radiographic evidence of SMV or portal vein distortion	Distant metastases
Clear fat planes around the celiac axis, hepatic artery, and SMA	Greater than 180 degrees SMA encasement, any celiac abutment
Borderline resectable	Unreconstructable SMV/portal occlusion
No distant metastases	Aortic or inferior vena cava invasion or encasement
Venous involvement of the SMV or portal vein with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal, allowing for safe resection and replacement	Body
Gastroduodenal artery encasement up to the hepatic artery with short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis	Distant metastases
Tumor abutment of the SMA not to exceed greater than 180 degrees of the circumference of the vessel wall	SMA or celiac encasement greater than 180 degrees
	Unreconstructable SMV/portal occlusion
	Aortic invasion
	Tail
	Distant metastases
	SMA or celiac encasement greater than 180 degrees
	Nodal status
	Metastases to lymph nodes beyond the field of resection should be considered unresectable

SMA = superior mesenteric artery; SMV = superior mesenteric vein.

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and overall survival.³¹ Recent studies have also evaluated combination chemoradiation therapy with FOLFIRINOX (fluorouracil/leucovorin/oxaliplatin/irinotecan), showing improvements in medial progression-free and medial overall survival rates compared with gemcitabine alone.^{30,32} However, the toxicity profile of irinotecan may limit its use.

For patients with locally advanced lesions or metastasis, the National Comprehensive Cancer Network panel recommends gemcitabine monotherapy because it may relieve symptoms.³ It also provides clinical benefit and modest survival benefit (two to three months).³⁰⁻³³ Second-line therapy involves combinations of gemcitabine with other agents such as fluorouracil, cisplatin, and oxaliplatin (Eloxatin).³

Intensity-modulated radiotherapy and stereotactic body radiotherapy are two techniques of radiation therapy aimed at increasing the dose to the tumor while sparing radiation to nearby healthy tissue. However, there is no established standard dosage of radiation regimen for either of these techniques.³⁴ The decision on whether to choose up-front chemoradiation or induction chemotherapy followed by consolidation chemoradiation should be based on disease response and patient tolerance. Three phase II trials have assessed up-front chemoradiation in locally advanced cancer with median survival rates ranging from 8.2 to 9 months.³

Because the most recent phase III trials improve survival by only several months (PRODIGE 4/ACCORD 11 median overall survival of 10.5 months vs. 6.9 months),³⁵ the treatment of advanced disease remains controversial. Management of pancreatic ductal adenocarcinomas should be approached from a multidisciplinary stance, with consideration of enrollment in clinical studies, and with goals of care and palliation routinely reassessed.

PALLIATIVE CARE

Palliative care for patients with locally advanced and metastatic disease should address symptoms from biliary obstruction, gastric outlet obstruction, cancer-related pain, malnutrition, thromboembolic disease, and depression. Pain intensity should be quantified and reassessed at specific intervals to determine effectiveness of therapies.³⁶ Early referral to hospice for appropriate patients is important, while they can best benefit from these services.

disease status to resectable. Postresection, these patients have survival rates similar to those with disease initially determined to be resectable.³

LOCALLY ADVANCED LESIONS AND METASTASIS

The primary goals of treatment for advanced pancreatic cancers are palliation and improved survival. In some patients who have good performance status (i.e., adequate nutrition and pain control and patent biliary stent), some effect on survival may be achieved.

The National Comprehensive Cancer Network recommends systemic chemotherapy followed by consolidation chemoradiation therapy as a treatment option. Concurrent administration of gemcitabine or continuous fluorouracil with radiation is an acceptable regimen.³ A new chemotherapeutic agent, irinotecan (Camptosar), can be used for patients with metastatic pancreatic adenocarcinoma to improve progression-free

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
Pancreas protocol computed tomography is considered the standard for diagnosis and staging of pancreatic cancer.	C	14, 15
The decision on resectability requires multidisciplinary consultation, and distinction should be made between tumors that are resectable, borderline resectable, or unresectable.	C	20
Pancreatic resections should be performed at institutions that complete at least 15 of these surgeries annually.	B	22-26
Adjuvant chemotherapy with gemcitabine (Gemzar) or fluorouracil/leucovorin improves overall survival in patients with resected pancreatic ductal adenocarcinomas (two to three months).	B	28-30
Irinotecan (Camptosar), a new chemotherapeutic agent, is an option for patients with metastatic pancreatic adenocarcinoma to improve progression-free and overall survival.	B	31
For patients with locally advanced or metastatic pancreatic cancer, chemoradiotherapy with gemcitabine provides clinical benefit and modest survival improvement (two to three months).	B	30-33
Placement of endoscopic biliary or enteral stents for biliary and gastric outlet obstruction provides palliative relief for persons with unresectable pancreatic cancer.	B	37-40
For prevention of recurrent thromboembolic disease in persons with pancreatic cancer, low-molecular-weight heparin is preferred over warfarin (Coumadin).	B	42

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to <http://www.aafp.org/afpsort>.

An estimated 65% to 75% of patients with pancreatic cancer develop biliary obstruction.³⁷ An endoscopic biliary stent is the preferred treatment, with metal stents having a lower risk of recurrent biliary obstruction compared with plastic stents.³⁸

Approximately 10% to 25% of patients with pancreatic cancer have symptomatic gastric outlet obstruction.³⁷ For patients with a short life expectancy or poor performance status, an enteral stent can be placed. Patients with a life expectancy longer than three to six months can receive an open or laparoscopic gastrojejunostomy with or without a jejunostomy tube, but an enteral stent is also an option.^{39,40}

For exocrine pancreatic insufficiency, oral pancreatic enzyme replacement is recommended.⁴¹ Monitoring body weight is the most important clinical parameter to follow when treating pancreatic exocrine insufficiency.³

To prevent recurrent thromboembolic disease, low-molecular-weight heparin is preferred over warfarin (Coumadin).^{3,42} Finally, depression should be addressed for patients, families, and caregivers. Chaplaincy services should be offered to patients whose spirituality and religion play an important role.⁴³

Surveillance

Data on surveillance for patients with resected pancreatic cancer are limited. Expert consensus recommends history and physical examination every three to six months for two years, then annually.⁴⁴ Monitoring for recurrence with cancer antigen 19-9 levels, CT, and endoscopic ultrasonography every three to six months can also be considered, although there is limited evidence showing that earlier treatment leads to improved patient outcomes.⁴⁵

Data Sources: Published literature on this topic was identified by using PubMed (1995 through January 2012), the Cochrane Database of Systematic Reviews, U.S. Preventive Services Task Force, Clinical Evidence, Essential Evidence Plus, and the National Guideline Clearinghouse database. Keywords for search included pancreatic cancer, pancreatic cancer diagnosis, and pancreatic cancer treatment. In addition, we searched for guidelines and systematic reviews related to the diagnosis and management of pancreatic cancer. All guidelines were reviewed for evidence of potential conflict, which might influence the recommendation as well as the use of an evidence-based approach. Search dates: January 2013, and January 31, 2014.

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REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;62(1):10-29.
2. American Cancer Society. Cancer facts & figures 2011. <http://www.cancer.org/Research/CancerFactsFigures/CancerFactsFigures/cancer-facts-figures-2011>. Accessed March 16, 2012.
3. National Comprehensive Cancer Network. NCCN clinical practice guideline in oncology. Pancreatic adenocarcinoma. Version 1.2014.

- http://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf [subscription required]. Accessed February 25, 2014.
4. Lochan R, Daly AK, Reeves HL, Charnley RM. Genetic susceptibility in pancreatic ductal adenocarcinoma. *Br J Surg*. 2008;95(1):22-32.
5. Ojajärvi IA, Partanen TJ, Ahlbom A, et al. Occupational exposures and pancreatic cancer: a meta-analysis. *Occup Environ Med*. 2000;57(5):316-324.
6. Brand RE, Lerch MM, Rubinstein WS, et al.; Participants of the Fourth International Symposium of Inherited Diseases of the Pancreas. Advances in counseling and surveillance of patients at risk for pancreatic cancer. *Gut*. 2007;56(10):1460-1469.
7. Screening for pancreatic cancer: recommendation statement. February 2004. <http://www.uspreventiveservicestaskforce.org/3rduspstf/pancreatic/pancrers.htm>. Accessed February 10, 2014.
8. Stoita A, Penman ID, Williams DB. Review of screening for pancreatic cancer in high risk individuals. *World J Gastroenterol*. 2011;17(19):2365-2371.
9. Krech RL, Walsh D. Symptoms of pancreatic cancer. *J Pain Symptom Manage*. 1991;6(6):360-367.
10. DiMaggio EP. Cancer of the pancreas and biliary tract. In: Winawer SJ, ed. *Management of Gastrointestinal Diseases*. New York, NY: Gower Medical Publishing; 1992:28.9
11. American Gastroenterological Association medical position statement: epidemiology, diagnosis, and treatment of pancreatic ductal adenocarcinoma. *Gastroenterology*. 1999;117(6):1463-1484.
12. Girelli CM, Reguzzoni G, Limido E, Savastano A, Rocca F. Pancreatic carcinoma: differences between patients with or without diabetes mellitus. *Recenti Prog Med*. 1995;86(4):143-146.
13. Palpation and percussion of the abdomen. In: McGee SR. *Evidence-Based Physical Diagnosis*. Philadelphia, Pa.: Saunders; 2001:1-4.
14. Klaus M, Schöbinger M, Wolf I, et al. Value of three-dimensional reconstructions in pancreatic carcinoma using multidetector CT: initial results. *World J Gastroenterol*. 2009;15(46):5827-5832.
15. Wong JC, Lu DS. Staging of pancreatic adenocarcinoma by imaging studies. *Clin Gastroenterol Hepatol*. 2008;6(12):1301-1308.
16. Oh HC, Kim MH, Hwang CY, et al. Cystic lesions of the pancreas: challenging issues in clinical practice. *Am J Gastroenterol*. 2008;103(1):229-239.
17. Safi F, Roscher R, Bittner R, Schenkluhn B, Dopfer HP, Beger HG. High sensitivity and specificity of CA 19-9 for pancreatic carcinoma in comparison to chronic pancreatitis. Serological and immunohistochemical findings. *Pancreas*. 1987;2(4):398-403.
18. Edge SB, American Joint Committee on Cancer. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.
19. National Cancer Institute. SEER stat fact sheets: pancreas cancer. <http://seer.cancer.gov/statfacts/html/pancreas.html>. Accessed March 16, 2012.
20. Li D, Xie K, Wolff R, Abbruzzese JL. Pancreatic cancer. *Lancet*. 2004;363(9414):1049-1057.
21. Callery MP, Chang KJ, Fishman EK, et al. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. *Ann Surg Oncol*. 2009;16(7):1727-1733.
22. Crist DW, Sitzmann JV, Cameron JL. Improved hospital morbidity, mortality, and survival after the Whipple procedure. *Ann Surg*. 1987;206(3):358-365.
23. Ho V, Heslin MJ. Effect of hospital volume and experience on in-hospital mortality for pancreaticoduodenectomy. *Ann Surg*. 2003;237(4):509-514.
24. Imperato PJ, Nenner RP, Starr HA, Will TO, Rosenberg CR, Dearie MB. The effects of regionalization on clinical outcomes for a high risk surgical procedure: a study of the Whipple procedure in New York State. *Am J Med Qual*. 1996;11(4):193-197.
25. Lieberman MD, Kilburn H, Lindsey M, Brennan MF. Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy. *Ann Surg*. 1995;222(5):638-645.
26. Sosa JA, Bowman HM, Gordon TA, et al. Importance of hospital volume in the overall management of pancreatic cancer. *Ann Surg*. 1998;228(3):429-438.
27. Diener MK, Fitzmaurice C, Schwarzer G, et al. Pylorus-preserving pancreaticoduodenectomy (pp Whipple) versus pancreaticoduodenectomy (classic Whipple) for surgical treatment of periampullary and pancreatic carcinoma. *Cochrane Database Syst Rev*. 2011;(5):CD006053.
28. Neoptolemos JP, Stocken DD, Friess H, et al.; European Study Group for Pancreatic Cancer. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer [published correction appears in *N Engl J Med*. 2004;351(7):726]. *N Engl J Med*. 2004;350(12):1200-1210.
29. Sohn TA, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg*. 2000;4(6):567-579.
30. Gourgou-Bourgade S, Bascoul-Molevi C, Desseigne F, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. *J Clin Oncol*. 2013;31(1):23-29.
31. Mornex F, Girard N, Delpero JR, Partensky C. Radiochemotherapy in the management of pancreatic cancer—part I: neoadjuvant treatment. *Semin Radiat Oncol*. 2005;15(4):226-234.
32. Conroy T, Desseigne F, Ychou M, et al.; Groupe Tumeurs Digestive of Unicancer; PRODIGE Intergrgroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817-1825.
33. Quiros RM, Brown KM, Hoffman JP. Neoadjuvant therapy in pancreatic cancer. *Cancer Invest*. 2007;25(4):267-273.
34. Chang DT, Schellenberg D, Shen J, et al. Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. *Cancer*. 2009;115(3):665-672.
35. Conroy T, Desseigne F, Ychou M, et al. Randomized phase III trial comparing FOLFIRINOX (F: 5FU/leucovorin [LV], irinotecan [I], and oxaliplatin [O]) versus gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma (MPA): preplanned interim analysis results of the PRODIGE 4/ACCORD 11 trial. *J Clin Oncol*. 2010;28(15 suppl; abstr 4010).
36. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Adult cancer pain. http://www.nccn.org/professionals/physician_gls/pdf/pain.pdf [subscription required]. Accessed February 25, 2014.
37. House MG, Choti MA. Palliative therapy for pancreatic/biliary cancer. *Surg Clin North Am*. 2005;85(2):359-371.
38. Moss AC, Morris E, Mac Mathuna P. Palliative biliary stents for obstructing pancreatic carcinoma. *Cochrane Database Syst Rev*. 2006;(2):CD004200.
39. Jeurnink SM, Steyerberg EW, Hof G, van Eijck CH, Kuipers EJ, Siersema PD. Gastrojejunostomy versus stent placement in patients with malignant gastric outlet obstruction: a comparison in 95 patients. *J Surg Oncol*. 2007;96(5):389-396.
40. Jeurnink SM, van Eijck CH, Steyerberg EW, Kuipers EJ, Siersema PD. Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review. *BMC Gastroenterol*. 2007;7:18.
41. Sikkens EC, Cahen DL, Kuipers EJ, Bruno MJ. Pancreatic enzyme replacement therapy in chronic pancreatitis. *Best Pract Res Clin Gastroenterol*. 2010;24(3):337-347.
42. Lee AY, Levine MN, Baker RI, et al.; Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med*. 2003;349(2):146-153.
43. Holland JC, Alici Y. Management of distress in cancer patients. *J Support Oncol*. 2010;8(1):4-12.
44. Tempero MA, Arnoletti JP, Behrman S, et al.; NCCN Pancreatic Adenocarcinoma Panel Members. Pancreatic adenocarcinoma. *J Natl Compr Canc Netw*. 2010;8(9):972-1017.
45. Sheffield KM, Crowell KT, Lin YL, Djukom C, Goodwin JS, Riall TS. Surveillance of pancreatic cancer patients after surgical resection. *Ann Surg Oncol*. 2012;19(5):1670-1677.

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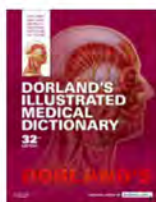
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Trav-a-tan (trav'ə-tan") trademark for a preparation of travoprost.

trav-o-prost (trav'o-prost) a synthetic prostaglandin analogue used in the treatment of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension; administered topically to the conjunctiva.

tray (tra) a flat-surfaced utensil for the conveyance of various objects or material.

acrylic resin t. an impression tray made of acrylic resin.

impression t. a horseshoe-shaped receptacle made of metal or other suitable material used to carry the impression material to the mouth, to confine the material in apposition to the surfaces to be recorded, and to control the impression material while it sets to form the impression.

tra-zo-done hy-dro-chlo-ride (tra'zo-dōn) [USP] an antidepressant used to treat major depressive episodes with or without prominent anxiety; administered orally.

Trea-cher Col-lins syndrome (tre'chər kol'inz) [Edward Treacher Collins, British surgeon, 1862–1932] see under *syndrome*.

Trea-cher Col-lins-Fran-ce-schet-ti syndrome (tre'chər kol'inz frahn'cha-sket'e) [E. Treacher Collins; Adolphe Franceschetti, Swiss ophthalmologist, 1896–1968] mandibulofacial dysostosis; see under *dysostosis*.

tread (tred) injury of the coronet of a horse's hoof, such as from being repeatedly struck with the shoe of the opposite side.

treat-ment (trēt'mənt) the management and care of a patient for the purpose of combating disease or disorder. See also under *care*, *maneuver*, *method*, *technique*, *test*, and *therapy*.

active t. curative t.

causal t. treatment directed against the cause of a disease.

conservative t. treatment designed to avoid radical medical therapeutic measures or operative procedures; often reserved for elderly or debilitated patients.

curative t. treatment designed to cure an existing disease, as opposed to *palliative t.* Called also *active t.*

drug t. pharmacotherapy.

electroconvulsive t., electroshock t. see under *therapy*.

empiric t. treatment by means which experience has proved to be beneficial.

expectant t. treatment designed only to relieve untoward symptoms, leaving the cure mainly to nature.

fever t. pyretotherapy.

Goeckerman t. treatment of psoriasis by applying ointments of tar followed by irradiation with ultraviolet B.

Hartel t. alcoholic injection for trigeminal neuralgia in which the needle is passed through the mouth into the region of the foramen ovale of the sphenoid bone.

medicinal t. pharmacotherapy.

neurodevelopmental t. Bobath method.

palliative t. treatment designed to relieve pain and distress, but not attempting a cure. See also *curative t.* Called also *supportive t.* and *palliative care*.

preventive t., prophylactic t. prophylaxis.

root canal t. see under *therapy*.

slush t. the treatment of acne by the application of a mixture of carbon dioxide snow, acetone, and sulfur.

specific t. treatment particularly adapted to a given disease.

supporting t., supportive t. palliative t.

surgical t. therapy using chiefly surgical methods. Cf. *pharmacotherapy* and *physical therapy*.

symptomatic t. expectant t.

Trec-a-tor (trek'ə-tor) trademark for a preparation of ethionamide.

tree (tre) 1. a perennial of the plant kingdom characterized by having a main stem or trunk and numerous branches. 2. something resembling such a plant, such as an anatomical structure that has branches. Called also *arbor*.

bronchial t. arbor bronchialis.

chaste t. 1. *Vitex agnus-castus*, a shrub native to the Mediterranean region, having blue or pink flowers and reddish black berries. 2. [USP] an extract prepared from the berries and root bark of *V. agnus-castus*, used for the symptomatic treatment of premenstrual syndrome and menopause; it is also used in homeopathy.

decision t. a graph resembling a tree in having an increasingly more complex branching structure flowing off an initial stem or point; used in decision analysis (q.v.) to represent choices and outcomes as the results of series of sequential decisions.

dendritic t. the branching arrangement of a dendrite.

tea t. *Melaleuca alternifolia*, a tree native to eastern Australia; its leaves and branches yield tea tree oil.

tracheobronchial t. the trachea and the bronchial tree considered as a unit.

tree-in-bud (tree-in-bud') exhibiting a pattern of centrilobular nodular and branching linear opacities, resembling a tree in bud; a nonspecific radiographic finding seen in a number of pulmonary conditions.

tre-foil (tre'foyl) 1. clover; see *Trifolium*. 2. any of various cloverlike plants, such as certain species of *Medicago* and *Lotus*.

bird's foot t. 1. *Lotus americanus*. 2. *Lotus corniculatus*.

burr t. *Medicago polymorpha*.

Treg T-regulatory; see *regulatory T cells*, under *cell*.

α,α-tre-hal-ase (tre-ha'lās) [EC 3.2.1.28] an enzyme of the hydrolase class that catalyzes cleavage of the glycosidic bond in trehalose to yield two molecules of glucose. Deficiency of the enzyme, an autosomal recessive disorder, causes trehalose malabsorption, which may be manifested as vomiting and diarrhea after ingestion of large amounts of edible mushrooms.

tre-ha-lose (tre-ha'lōs) a disaccharide occurring mainly in insects, algae, and some mushrooms; when hydrolyzed by acids or enzymes it yields glucose.

Treitz arch, hernia, etc. (trīts) [Wenzel Treitz, Czech physician, 1819–1872] see under *arch* and *hernia* and see *musculus suspensorius duodeni* and *recessus duodenalis superior*.

Trel-star (trel'stahr) trademark for a preparation of triptorelin pamoate.

Trem-a-to-da (trem'ə-to'da) [Gr. *trēmātōdēs* pierced] the flukes, a class of the phylum Platyhelminthes. Most are parasitic, with animals becoming infected by eating uncooked or undercooked fish, crustaceans, or vegetation. All flukes require a mollusk as their first intermediate host, in which a complex developmental cycle takes place. The larval stage, which escapes from the mollusk, may either enter a second intermediate host (fish, crustacean, or another mollusk), encyst on vegetation, or penetrate directly into the skin of the definitive host. Important trematodes infecting humans belong to the genera *Clonorchis*, *Dicrocoelium*, *Echinostoma*, *Fasciola*, *Fasciolopsis*, *Gastrodiscoides*, *Heterophyes*, *Metagonimus*, *Opisthorchis*, *Paragonimus*, and *Schistosoma*.

trem-a-tode (trem'ə-tōd) any member of the class Trematoda; called also *fluke*.

trem-a-to-di-a-sis (trem'ə-to-di'ə-sis) infection with trematodes.

trem-ble (trem'bəl) [L. *tremulus* trembling] to shake or quiver involuntarily, as with anger or fear.

trem-bles (trem'bəlz) 1. any of various neurological diseases of domestic animals in which tremors are a prominent symptom. 2. poisoning in cattle and sheep that feed on the plants *Eupatorium rugosum* and *Haplopappus heterophyllus*, which contain the toxin tremetol; the animal has muscular tremors, becomes weak, and may suddenly stumble and fall. Humans who consume milk, milk products, or flesh from an animal so affected may develop the acute condition called *milk sickness*.

congenital t. congenital tremor syndrome.

trem-el-loid (trem'ə-loid) like jelly; gelatinous.

tre-mel-lose (trem'ə-lōs) tremelloid.

trem-e-tol (trem'ə-tol) a toxin found in the white snakeroot, *Eupatorium rugosum*, and the rayless goldenrod, *Haplopappus heterophyllus*, which causes trembles in cattle and sheep and milk sickness in humans. Called also *tremetone*.

trem-e-tone (trem'ə-tōn) tremetol.

tre-mo-gram (tre'mo-gram) [tremor + -gram] the tracing or record made by a tremograph; a graphic tracing of a tremor. See *ataxiometer*.

tre-mo-graph (tre'mo-graf) [tremor + -graph] an instrument for recording tremors.

trem-or (trem'ər) [L., from *tremere* to shake] an involuntary trembling or quivering. **trem'ulous adj**

action t. rhythmic, oscillatory, involuntary motion of a part during voluntary movements, as of the outstretched upper limb when writing or lifting a cup. Called also *intention t.*, *kinetic t.*, *postural t.*, and *volitional t.*

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245 1 0 a| European journal of cancer h| [electronic resource].

246 1 i| Title on image of cover: a| EJC f| <2003->

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260 3 3| <2011-> : a| Oxford : b| Elsevier

310 a| 18 times a year, b| 2000-

321 a| Frequency varies, b| <1995>-1999

362 1 a| Print began with vol. 26, issue 1 (Jan. 1990).

515 a| Issues for <v. 31, issue 1 (1995)>-v. 32, issue 14 (Dec. 1996) called also <v. 31A no. 1>-v. 32A, no. 14.

538 a| Mode of access: World Wide Web.

550 a| Official Journal of EORTC, ESO, EACR, FECS and EUSOMA, <2003->; ECCO <2011->

588 a| Description based on: Vol. 26, issue 1 (Jan. 1990); title from PDF editorial board page (ScienceDirect, viewed Oct. 22, 2010).

588 a| Latest issue consulted: Vol. 46, issue 16 (Nov. 2010) (ScienceDirect, viewed Oct. 22, 2010).

588 a| Latest issue consulted: V. 48, issue 4 (Mar. 2012) (ScienceDirect, viewed Mar. 7, 2012).

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650 0 a| Cancer x| Periodicals.

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650 2 a| Neoplasms v| Periodicals.

650 2 a| Neoplasms x| periodicals.

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653 0 0 a| oncologie

653 0 0 a| oncology

653 1 0 a| Human Pathology

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655 0 a| Electronic journals.

710 2 a| European Organization for Research on Treatment of Cancer. 1| <https://id.oclc.org/worldcat/entity/E39QH7JmrXwC6Gy7HccHqCDbM6>.710 2 a| European School of Oncology. 1| <https://id.oclc.org/worldcat/entity/E39QQPVp7XKckhPTrytMv3YwdF>.710 2 a| European Association for Cancer Research. 1| <https://id.oclc.org/worldcat/entity/E39QH7JmqQmGbhD7cpkWcc7b9t>.710 2 a| Federation of European Cancer Societies. 1| <https://id.oclc.org/worldcat/entity/E39QH7JmqfryV9Vp6B1YY9>.

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Published	1990- : [Oxford] ; [New York] : Pergamon Pres Ltd., 1990- <2011-> : Oxford : Elsevier
Additional Creators	European Organization for Research on Treatment of Cancer , European School of Oncology , European Association for Cancer Research , Federation of European Cancer Societies , European Society of Mastology , and European CanCer Organisation

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Issues for -v. 32, issue 14 (Dec. 1996) called also -v. 32A, no. 14.

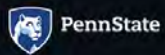
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362 1 a| Began with Volume 1, Issue 1 (January 2016).

538 a| Mode of access: World Wide Web.

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588 a| Latest issue consulted: Volume 4, Issue 2 (August 2018) (viewed November 26, 2018).

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Appendix ERASLAN02

Original Article

First line modified Folfirinox versus gemcitabine for advanced pancreatic cancer: A single institution retrospective experience

Emrah Eraslan ^{a,*}, Fatih Yildiz ^a, Gulnihal Tufan ^a, Ferit Aslan ^b, Umut Demirci ^a, Omur Berna Oksuzoglu ^a^a University of Health Sciences, Dr. A.Y Ankara Oncology Education and Research Hospital, Department of Medical Oncology, Yenimahalle, Ankara, Turkey^b Siirt Government Hospital, Siirt, Turkey

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ABSTRACT

Background: Advanced pancreatic cancer (APC) is a highly lethal malignancy which has one of the worst treatment outcomes. Modified (m)FOLFIRINOX is an intense but a proven treatment approach with a survival benefit for APC. Although mFOLFIRINOX demonstrated survival benefit compared with gemcitabine monotherapy, the standard treatment in previous years, toxicity is a difficult aspect of this treatment.

Methods: A retrospective analysis of patients referred to Medical Oncology Clinics of Ankara Oncology Research and Training Hospital with the diagnosis of inoperable locally advanced or metastatic pancreatic cancer and treated with mFOLFIRINOX or gemcitabine monotherapy from March 2013 to April 2018 was performed.

Results: Forty three patients and 37 patients were included in mFOLFIRINOX and gemcitabine groups, respectively. The mean age of the patients was 53.74 years (range: 32–69) and 65.7 years (range: 47–82) for mFOLFIRINOX and gemcitabine, respectively (95% CI, $p < 0.001$). All patients, except one, had ECOG performance status of 0 or 1 in mFOLFIRINOX group. In contrast, nine patients had ECOG performance status of 2 in the gemcitabine group (95% CI, $p = 0.002$). When the patients were evaluated for response, 11 (25.6%) and 6 (16.2%) had partial remission with mFOLFIRINOX and gemcitabine, respectively. Median PFS and OS was 5.73 (95% CI, 2.57–8.90) months and 8.77 (95% CI, 6.54–10.99) months with mFOLFIRINOX and 2.77 (95% CI, 2.29–3.24) months and 5.80 (95% CI, 3.08–7.92) months with gemcitabine, respectively. mFOLFIRINOX regimen was more toxic than gemcitabine regimen. The incidences of all-grade neutropenia, neuropathy, and emesis were more prominent in the mFOLFIRINOX group.

Conclusion: mFOLFIRINOX is a difficult regimen for both patients and physicians with significant toxicity with a greater survival benefit. The survival benefit was modest in this real-life experience. Patient selection bias and small sample size of this retrospective study should be considered.

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1. Introduction

Advanced pancreatic cancer (APC) is a highly lethal malignancy which has one of the worst treatment outcomes. According to GLOBOCAN data, the incidence and mortality rates were detected as 4.5 and 4.3 per hundred thousand respectively in Turkey in 2012.¹ Nearly half of the patients have metastatic disease at the time of diagnosis; with a 5-year overall survival (OS) rate of only 2.7%.² For many years, gemcitabine-based chemotherapy (usually

single-agent gemcitabine) has been recommended in the metastatic stage. Nevertheless, more promising results have been reported recently with new combination chemotherapies. In phase 3 PRODIGE study comparing FOLFIRINOX (5-FU, Irinotecan, and Oxaliplatin) combined chemotherapy with gemcitabine monotherapy, overall survival was found to be 11.1 months versus 6.8 months respectively. However, a significant increase in toxicity in combination arm was also reported.³ In the phase 3 MPACT trial in which the combination therapy of nab-paclitaxel-gemcitabine was compared with single-agent gemcitabine treatment, OS was found to be 8.5 months versus 6.7 months.⁴ Nowadays, these new combination treatments have become frequently preferred in routine practice.

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In two recent phase 2 studies, less toxicity was observed with FOLFIRINOX, administered by modifying the doses of chemotherapeutics, with a similar OS to standard-dose treatment.^{5,6} In another study with 102 patients with advanced stage pancreatic cancer (APC), similar OS and progression-free survival (PFS) were observed in groups with and without dose modification.⁷

We aimed to show our experience with modified FOLFIRINOX and gemcitabine as first-line therapy in patients with metastatic or unresectable locally advanced pancreatic cancer.

2. Material and method

A retrospective analysis of patients who referred to Medical Oncology Clinics of Ankara Oncology Research and Training Hospital with the diagnosis of inoperable locally advanced or metastatic pancreatic cancer and treated with mFOLFIRINOX (Oxaliplatin 65 mg/m² IV on day 1, Irinotecan 135 mg/m² IV on day 1, Fluorouracil (FU) 2400 mg/m² IV infusion over 46 h on day 1, every 2 weeks) or gemcitabine monotherapy (1000 mg/m² IV on 1. and 8. days, every 21 days) from March 2013 to April 2018 was performed. Hospital registry system data, patient files, laboratory and radiological records were retrospectively screened. Only the patients with pancreatic adenocarcinoma histology were included in the study; other histological types were excluded. Patients who

received a treatment regimen other than mFOLFIRINOX or gemcitabine as first-line treatment were not included in the study also. Patients were evaluated for demographic characteristics, the number of chemotherapy cycles, side effects, dose reductions, granulocyte colony-stimulating factor (G-CSF) use, presence/absence of neutropenic fever, radiological response, PFS and OS data. IRB approval has not received.

2.1. Statistical analysis

SPSS 24.0 (Statistical Package for Social Sciences, Chicago, IL, USA) was used for statistical analysis. Pearson Chi-square test was used for comparison of nonparametric categorical variables. Mann-Whitney test was used for comparison of nonparametric numerical variables. Kaplan-Meier method was used for survival analysis; statistical differences were evaluated by Log-rank test. A value of $p < 0.05$ was considered significant. We did a Cox regression analysis for overall survival.

3. Results

3.1. General features

General patient characteristics are given in Table 1a. There were 10 (12.5%) patients who had curative surgery before and subsequently advanced to the metastatic stage.

Mean age of patients were 53.74 (95% CI: 33–69) in mFOLFIRINOX group and 65.70 (95% CI: 47–82) in gemcitabine group ($p < 0.001$). Forty-two (97.7%) patients in mFOLFIRINOX group and 28 (75.7%) patients in gemcitabine group had an ECOG PS score of 0 or 1 ($p = 0.003$). Twenty-nine (67.4%) patients in mFOLFIRINOX group and 26 (70.3%) patients in the gemcitabine group had liver metastasis. Liver was the most metastatic site for both groups. Mean basal concentrations of CA 19.9 were 13747 U/mL and 4566 U/mL for mFOLFIRINOX and gemcitabine groups, respectively ($p = 0.040$). Both groups were similar in terms of other patient characteristics (Table 1b).

3.2. Efficacy

Findings related to treatment are stated in Table 2.

Median PFS and OS was 5.73 (95% CI: 2.57–8.90) months and 8.77 (95% CI: 6.54–10.99) months with mFOLFIRINOX and 2.77 (95% CI: 2.29–3.24) months and 5.80 (95% CI: 3.08–7.92) months with gemcitabine, respectively (Fig. 1).

In the univariate analysis for OS, the total number of cycles over five affected survival positively ($p < 0.001$, HR:0.30, 95% CI: 0.18–0.50). No significant difference was seen for performance score and age (Table 3).

Table 1a
General patient characteristics.

	n = 80 (%)
Age-year (range)	60 (33–82)
Gender	
Male	57 (71.2%)
Female	23 (28.8%)
Cigarette smoking	
Yes	38 (47.5%)
No	42 (52.5%)
Alcohol	
Yes	12 (15%)
No	68 (85%)
Tumor location	
Head	43 (53.8%)
Body	25 (31.2%)
Tail	12 (15%)
ECOG PS	
0	9 (11.3%)
1	61 (76.2%)
2	10 (12.5%)
Stage	
Locally advanced	14 (17.5%)
Metastatic	66 (82.5%)
Previous operation	
No	70 (87.5%)
Yes	10 (12.5%)
Chemotherapy	
mFOLFIRINOX	43 (53.7%)
Gemcitabine	37 (46.3%)

Table 1b
General patient characteristics.

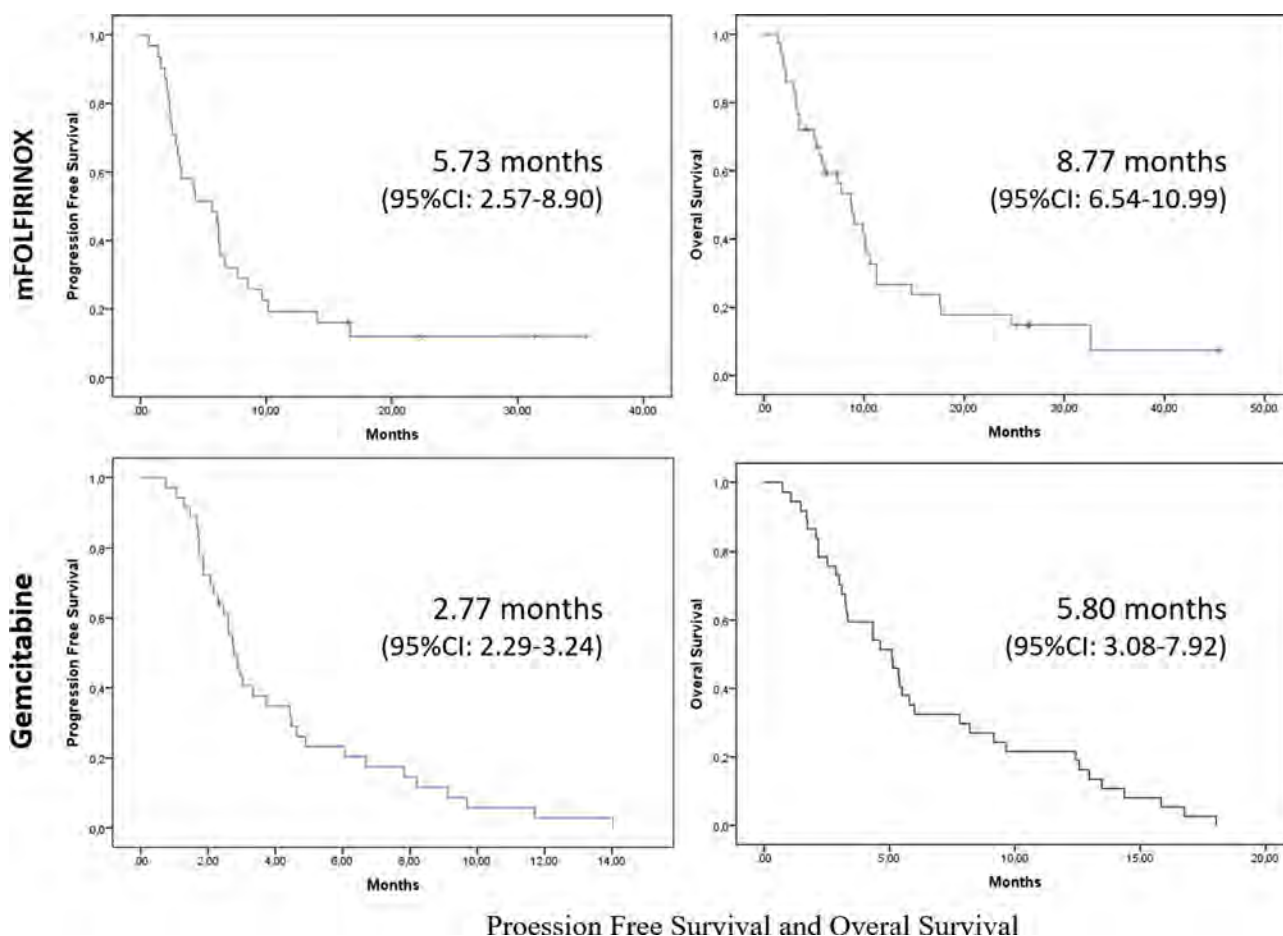
	mFOLFIRINOX (n = 43)	Gemcitabine (n = 37)	p
Age-year (range)	53.74 (33–69)	65.70 (47–82)	<0.001
Gender (male/female)	33 (76.7%)/10 (23.3%)	24 (64.9%)/13 (35.1%)	0.242
ECOG PS (0–1)	42 (97.7%)	28 (75.7%)	0.003
Non-Comorbidities	26 (60.5%)	15 (40.5%)	0.153
Cigarette smoking	24 (55.8%)	13 (35.1%)	0.125
Alcohol	8 (18.6%)	3 (8.1%)	0.208
Basal CA 19.9 (mean, U/mL)	13747	4566	0.040
More than one metastatic site	18 (41.8%)	19 (51.9%)	0.286
Locally Advanced Disease	8 (18.6%)	6 (16.2%)	0.779

Table 2

Findings related to treatment.

	mFOLFIRINOX (n = 43)	Gemcitabine (n = 37)	p
Number of cycles	8 (1–30)	3 (1–9)	
Dose Reduction	13 [30.2% (10–30)]	6 [16.2% (10–20)]	0.098
GCSF usage	10 (23.3%)	1 (2.7%)	0.006
Second-line treatment	14 (32.6%)	7 (18.9%)	0.001
Objective Response (Radiologic PR)	11 (25.6%)	6 (16.2%)	0.512
Clinical Benefit (Radiological PR + SD)	26 (60.5%)	14 (37.8%)	0.094

GCSF: Granulocyte Colony Stimulating Factor, PR: Partial Response, SD: Stable Disease, findings except number of cycles is given as the number of patients.

**Fig. 1.** Progression free survival and overall survival.

3.3. Side effects

Side effects of anemia, thrombocytopenia, diarrhea, and fatigue were more frequent in the mFOLFIRINOX group, but both groups were similar in terms of statistical significance. Statistical analysis was not performed for grade 3–4 side effects due to the inadequate number of events (Table 4). No treatment-related mortality was observed in both groups.

Table 3

Univariate analysis for OS.

	p	HR	%95 CI
Age (Lowest 60)	0.35	0.34	0.49–1.28
Number of Cycle (Lowest 5)	<0.001	0.30	0.18–0.50
ECOG (0–1)	0.95	0.98	0.4–1.9

4. Discussion

In our study, PFS (5.73 months - 2.77 months) and OS (8.77 months - 5.80 months) were better in the mFOLFIRINOX group than gemcitabine group. In addition, overall survival was only affected by the number of chemotherapy cycles. In a phase 3 trial comparing gemcitabine with 5-fluorouracil in the treatment of advanced pancreatic cancer, OS (5.65 months vs. 4.41 months) was statistically significant in favor of gemcitabine.⁸ In addition, two meta-analyses showed that combination therapies of gemcitabine had borderline OS advantage compared to single-agent gemcitabine. Gemcitabine monotherapy had become standard therapy on this issue.^{9,10} FOLFIRINOX, one of the current treatment options, was found to be superior to gemcitabine with a fairly long OS of 11.1 months in phase 3 study.³ In our study, both PFS and OS were found to be better than gemcitabine monotherapy treatment. But,

Table 4
Side effects.

	All Grade Side Effects			Grade 3–4 Side Effects	
	mFOLFIRINOX (n = 43)	Gemcitabine (n = 37)	p	mFOLFIRINOX (n = 43)	Gemcitabine (n = 37)
Neutropenia	22 (51.2%)	9 (24.3%)	0.006	11 (25.6%)	4 (10.8%)
Neutropenic Fever				4 (9.3%)	0
Anemia	25 (58.1%)	16 (43.2%)	0.091	1 (2.3%)	1 (2.7%)
Thrombocytopenia	3 (7.0%)	3 (8.1%)	0.92	0	1 (2.7%)
Neuropathy	5 (11.6%)	0	0.026	1 (2.3%)	0
Nausea	21 (48.8%)	7 (18.9%)	0.002	1 (2.3%)	0
Diarrhea	10 (23.3%)	5 (13.5%)	0.204	4 (9.3%)	1 (2.7%)
Fatigue	28 (65.1%)	23 (62.2%)	0.467	6 (14.0%)	5 (13.5%)

survival benefit provided by mFOLFIRINOX was behind the literature and modest. The survival durations we found were better than the literature data of gemcitabine.^{8–10}

An inevitable result of combination therapy is the increased toxicity.³ The higher likelihood of toxicity predicted by mFOLFIRINOX in our study affected patient selection during treatment planning. Therefore, mFOLFIRINOX group was younger and had better ECOG performance score level. In addition, more chemotherapy cycles were applied to this group. These differences might have affected both PFS and OS durations. In our univariate analysis for OS, the total number of cycles over five affected survival positively. Probably because of the small number of patients, we did not see this significance in performance score and age. However, the ratio of objective response (radiological partial response) and the ratio of clinical benefit (radiological partial response and stable disease) were better in the mFOLFIRINOX group but the differences were not statistically significant. This may be due to the inadequate number of patients. But, the better radiological response suggests that the factor that is effective on PFS and OS is not patient selection alone. In addition, in our study PFS and OS were found to be shorter than PRODIGE study.³ This may be due to patient selection bias and the small number of patients. In a retrospective study, only one in four patients treated with FOLFIRINOX in real life was found to be in accordance with the inclusion criteria of phase 3 FOLFIRINOX study.¹¹ Similarly, in a retrospective real-life data from Japan, the OS was found to be 8.9 months with FOLFIRINOX. Moreover, in this study, no modification was made to the chemotherapy scheme.¹² In another retrospective Japanese study, OS was reported to be 11.1 months.¹³ Retrospective UK study reported PFS 7.2 months, OS 9.3 months and in another US retrospective study, OS was reported as 11.4 months.^{14,15} Differences in the literature can be explained by the retrospective nature of the studies, patient selection, and regional-racial differences. In this study, it is obvious that we have obtained PFS and OS benefit in accordance with the literature in the treatment of pancreatic cancer with mFOLFIRINOX treatment.

FOLFIRINOX is a treatment regimen in which intensive toxicity is expected. The basis of toxicity is hematological toxicity and associated neutropenic fever, and it has a wide range of toxicity with toxic deaths.^{3,12,13} In our study, when all side effects were taken into account, neutropenia, neuropathy, and nausea were significantly higher in the mFOLFIRINOX group. In addition, anemia, diarrhea, and fatigue were more common but not statistically significant.

In our study, all of the grade 3–4 hematological and non-hematological side effects were less frequent than in the PRODIGE study. In the PRODIGE study, 45.7% grade 3–4 neutropenia was observed. In our study, grade 3–4 neutropenia rate was 25.6%. Despite this, in PRODIGE study, 5.4% of neutropenic fever was observed whereas in our study this rate was 9.3%.³ In the PRODIGE study, 42.5% of patients were given prophylactic G-CSF, whereas in our study this was 23.3%. The reason why neutropenic fever was more frequent in our study could be the lack of use of G-CSF.

Furthermore, neutropenia and other side effects may be more likely to be determined, depending on the more strict follow-up in phase 3 studies. In the retrospective Japanese study, the neutropenic fever rate was found to be 13% higher than the PRODIGE study.¹² In two recent phase 2 studies, mFOLFIRINOX was used at similar doses to our study and less toxicity was observed with a similar OS to standard-dose treatment.^{5,6} It is clear that dose modification is effective in reducing side effects. However, as in the case of neutropenic fever, it should be kept in mind that prospective clinical trial data and daily life data may not coincide exactly. When we compare with the results of a meta-analysis involving 12 studies with modified FOLFIRINOX with our study; grade 3–4 neutropenia, fatigue, nausea, diarrhea, and neuropathy were similar with less anemia and thrombocytopenia in our study. However, the neutropenic fever was seen twice as often compared to the meta-analysis in our study.¹⁶ With the use of more intensive prophylactic G-CSF in daily practice, side effect profile similar to that of the literature can be provided.

The retrospective nature of our study and the low number of patients constitute the main limitations. The difference between the two groups in terms of basic features prevented a healthy comparison between the two groups. Similarly, the statistical evaluation for grade 3–4 side effects could not be made due to the small number of events.

5. Conclusion

In advanced pancreatic cancer patients with good ECOG PS, mFOLFIRINOX treatment provided OS and PFS benefit with manageable toxicity profile. Sustainability of treatment due to side effects is a major problem for both the patient and the physician. Dosage modification of the treatment scheme and the use of appropriate prophylactic G-CSF may provide a lower side effect profile with similar efficacy and better quality of life in the literature.

References

1. GLOBOCAN. Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. <http://publications.iarc.fr/Databases/Iarc-Cancerbases/GLOBOCAN-2012-Estimated-Cancer-Incidence-Mortality-And-Prevalence-Worldwide-In-2012-V1.0-2012>. Accessed September 28, 2018.
2. Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Pancreatic Cancer. <https://seer.cancer.gov/statfacts/html/pancreas.html>. Accessed September 28, 2018.
3. Conroy T, Desseigne F, Ychou M, et al. Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817–1825.
4. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369(18):1691–1703.
5. Ozaka M, Ishii H, Sato T, et al. A phase II study of modified FOLFIRINOX for chemotherapy-naïve patients with metastatic pancreatic cancer. *Cancer Chemother Pharmacol*. 2018;81(6):1017–1023.
6. Yoshida K, Iwashita T, Uemura S, et al. A multicenter prospective phase II study of first-line modified FOLFIRINOX for unresectable advanced pancreatic cancer.

- Oncotarget*. 2017;8(67):111346–111355.
7. Chhanna MK, Cook N, Dhani NC, et al. FOLFIRINOX for advanced pancreatic cancer: the princess margaret cancer centre experience. *Br J Canc*. 2016;115(6):649–654.
 8. Burris 3rd HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol*. 1997;15(6):2403–2413.
 9. Ciliberto D, Botta C, Correale P, et al. Role of gemcitabine-based combination therapy in the management of advanced pancreatic cancer: a meta-analysis of randomised trials. *Eur J Cancer*. 2013;49(3):593–603.
 10. Sun C, Ansari D, Andersson R, Wu DQ. Does gemcitabine-based combination therapy improve the prognosis of unresectable pancreatic cancer? *World J Gastroenterol*. 2012;18(35):4944–4958.
 11. Ho MY, Kennecke HF, Renouf DJ, et al. Defining eligibility of FOLFIRINOX for first-line metastatic pancreatic adenocarcinoma (MPC) in the province of British columbia: a population-based retrospective study. *Am J Clin Oncol*. 2017;40(6):552–554.
 12. Tahara J, Shimizu K, Otsuka N, et al. Gemcitabine plus nab-paclitaxel vs. FOLFIRINOX for patients with advanced pancreatic cancer. *Cancer Chemother Pharmacol*. 2018;82(2):245–250.
 13. Todaka A, Mizuno N, Ozaka M, et al. Nationwide multicenter observational study of FOLFIRINOX chemotherapy in 399 patients with unresectable or recurrent pancreatic cancer in Japan. *Pancreas*. 2018;47(5):631–636.
 14. Ghorani E, Wong HH, Hewitt C, et al. Safety and efficacy of modified FOLFIRINOX for advanced pancreatic adenocarcinoma: a UK single-centre experience. *Oncology*. 2015;89(5):281–287.
 15. Cartwright TH, Parisi M, Espirito JL, et al. Clinical outcomes with first-line chemotherapy in a large retrospective study of patients with metastatic pancreatic cancer treated in a US community Oncology setting. *Drugs Real World Outcomes*. 2018;5(3):149–159.
 16. Tong H, Fan Z, Liu B, Lu T. The benefits of modified FOLFIRINOX for advanced pancreatic cancer and its induced adverse events: a systematic review and meta-analysis. *Sci Rep*. 2018;8(1):8666.

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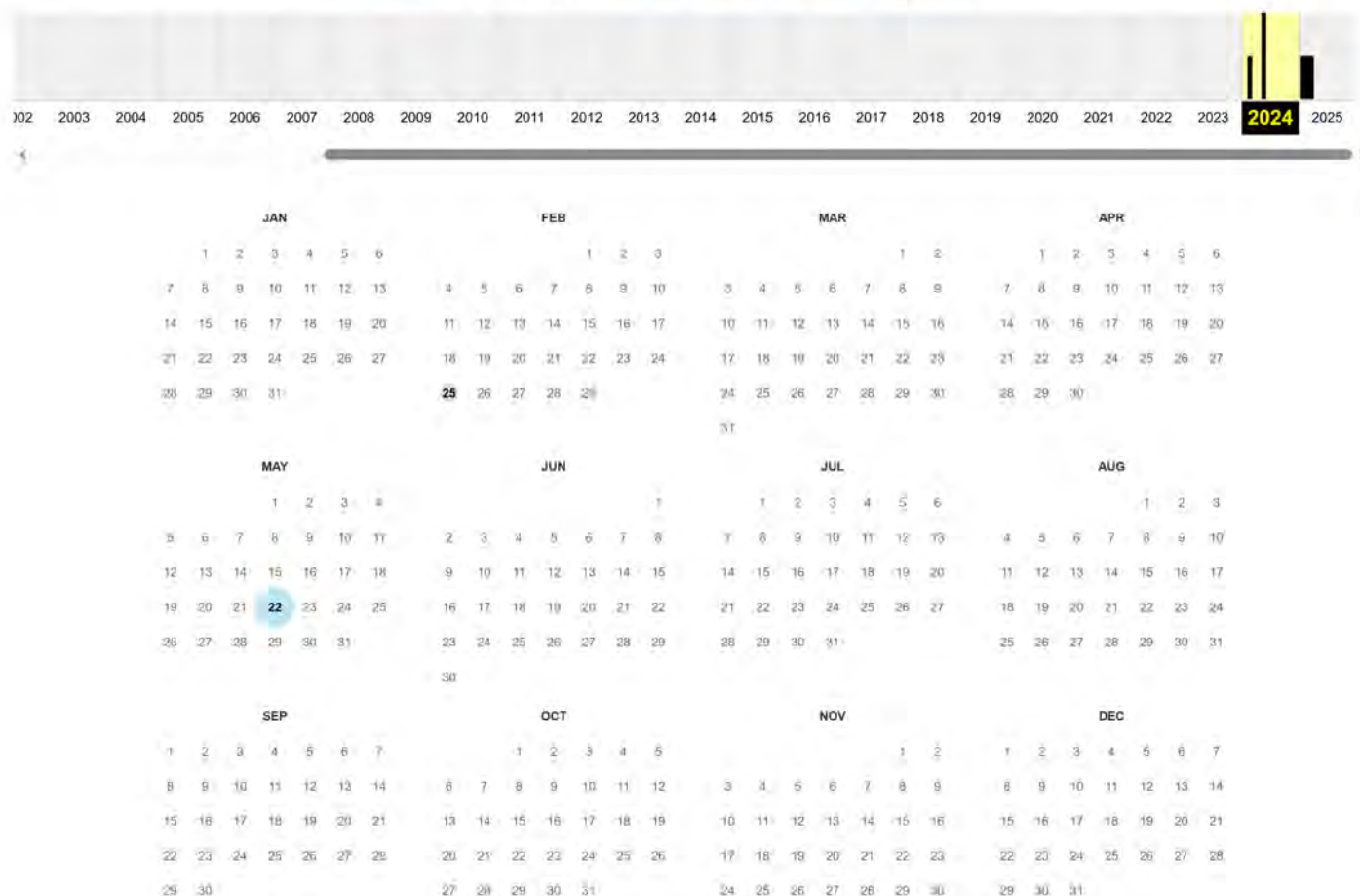
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NDA 207793/S-016

SUPPLEMENT APPROVAL

Ipsen Biopharmaceuticals, Inc.
Attention: Kirsten Overoye-Chan
Senior Director Global Regulatory Affairs
One Main Street, 7th Floor
Cambridge, MA 02142

Dear Kirsten Overoye-Chan:

Please refer to your April 13, 2023, supplemental new drug application (sNDA), received April 13, 2023, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Onivyde (irinotecan liposome injection) injection.

This Prior Approval supplemental new drug application provides for the new indication of Onivyde in combination with oxaliplatin, fluorouracil and leucovorin, for the first-line treatment of adult patients with metastatic pancreatic adenocarcinoma.

NDA 207793/S-016

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APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information), with the addition of any labeling changes in pending "Changes Being Effectuated" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible from publicly available labeling repositories.

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.³

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.⁴ Information and Instructions for completing the form can be found at FDA.gov.⁵

³ For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/media/128163/download>.

⁴ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

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PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Rebecca Cohen, Regulatory Health Project Manager, at (240) 402-4998.

Sincerely,

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Steven Lemery, M.D., M.H.S.
Director
Division of Oncology 3
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Appendix FONSECA02

Retrospective comparison of the efficacy and the toxicity of standard and modified FOLFIRINOX regimens in patients with metastatic pancreatic adenocarcinoma

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Background: FOLFIRINOX stands a major breakthrough in the management of metastatic pancreatic adenocarcinoma (MPA). Nonetheless, significant side-effects have been reported using standard FOLFIRINOX. We aimed to compare survival outcomes, response rates and toxicity of patients treated with standard or modified FOLFIRINOX in MPA.

Methods: We included patients aged ≥ 18 years old, with pathologically confirmed MPA, treated with FOLFIRINOX in the first-line setting. Patients submitted to at least one cycle of full-dose FOLFIRINOX were grouped in the standard FOLFIRINOX group.

Results: Patients treated with standard FOLFIRINOX were younger and had less comorbidity. We observed no differences in overall survival or in progression-free survival between the two treatment arms. The only variable independently associated with OS was $\log_{10}$ [neutrophil-to-lymphocyte ratio (NLR)]. Modified FOLFIRINOX was associated with a lower dose reduction rate, but a slightly increased incidence of severe toxicity.

Conclusions: Modified FOLFIRINOX presents the same activity against MPA as standard FOLFIRINOX. We found no significant differences in toxicity, possibly due to patient selection and a higher dose reduction rate in the standard FOLFIRINOX arm. NLR stood as an important prognostic marker and further research is needed to comprehend its biological meaning in pancreatic cancer.

Keywords: Metastasis; pancreas; carcinoma; therapeutics

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Introduction

Metastatic pancreatic adenocarcinoma (MPA) represents a highly lethal condition. At the population level, a median overall survival of 2 months and a 5-year survival rate of 3.7% have been reported (1,2). Until recently, treatment efficacy fell short of expectations even in the setting of controlled randomized trials, and no single study had been able to demonstrate clinically meaningful and statistically

significant benefits in overall survival of Gemcitabine-based combination chemotherapy over Gemcitabine alone (3). Thus, treatment improvements have been eagerly pursued in the management of MPA.

The randomized trial ACCORD 11/PRODIGE 4 stands as major breakthrough in the management of MPA. In this study, Conroy *et al.* were able to demonstrate benefits in median overall survival (11.1 *vs.* 6.8 months),

median progression-free survival (6.4 *vs.* 3.3 months) and overall response rate (31.6% *vs.* 9.4%) with the use of FOLFIRINOX when compared to Gemcitabine (4). Quality of life analysis also favored treatment with FOLFIRINOX (5). Moreover, these results have been further reproduced in a similar phase 3 trial held in India (6). Perhaps more importantly, the feasibility of FOLFIRINOX outside the setting of a clinical trial has been demonstrated and the survival figures of the pivotal trial have also been reproduced in the clinical practice (7,8).

Unfortunately, the incremental activity of FOLFIRINOX comes at the expense of increased toxicity. High rates of grades 3–4 neutropenia (45.7%), fatigue (23.6%), vomiting (14.5%) and diarrhea (12.7%) have been reported in ACCORD 11/PRODIGE 4. Also, the low rate of febrile neutropenia (5.4%) reported in this trial has not been confirmed in some investigations, particularly in Asian patients and in the real-world setting (9–11). Indeed, in the later scenarios, rates of febrile neutropenia slightly above 20% have been reported and, as a result, FOLFIRINOX is frequently administered in conjunction with granulocyte colony-stimulating factor (G-CSF). Besides, FOLFIRINOX has been tested in clinical trials in rather selected populations, comprised of relatively young and fit patients. Thus, concerns regarding the toxicity profile of standard FOLFIRINOX prompted the evaluation of modified (attenuated) FOLFIRINOX regimens.

Some studies have addressed the activity and toxicity of modified FOLFIRINOX in MPA. As a general rule, similar survival outcomes to those described in the FOLFIRINOX arm of the ACCORD 11/PRODIGE 4 study have been shown (7,12–16). Additionally, a more tolerable side-effect profile has been demonstrated. Nevertheless, there is a shortage of comparative studies evaluating the outcomes of patients treated with standard FOLFIRINOX or with modified FOLFIRINOX (7) as most investigators describe the activity and the toxicity of their modified FOLFIRINOX regimens while comparing their results with those achieved in the FOLFIRINOX arm of the pivotal trial. Also, except for two Asian investigations, all previous studies have used mixed populations consisting of patients with locally advanced and metastatic pancreatic cancer (14).

Hence, we undertook a retrospective study to evaluate differences in outcomes of patients with MPA treated with standard or with modified FOLFIRINOX as first-line treatment. Additionally, we evaluated potential prognostic factors for patients with MPA treated with FOLFIRINOX in 1st line.

Methods

Design

This is a retrospective study, performed in a single cancer-dedicated hospital in Brazil. It was based on routinely collected data extracted from electronic charts of patients with MPA submitted to first-line treatment with FOLFIRINOX. Data were collected from June 2017 to December 2017. This study was approved by the AC Camargo Cancer Center Internal Ethics Board Review (CAAE 822894.5.0000.5432).

Patients

Inclusion criteria encompassed: age ≥ 18 years old, pathologically confirmed diagnosis of pancreatic adenocarcinoma, ECOG performance status 0–2, previously untreated metastatic disease and treatment with at least one cycle of FOLFIRINOX in first-line from January 1st 2010 through December 31th 2016. We excluded patients treated outside AC Camargo Cancer Center and those with concomitant metastatic malignancies. Patients submitted to at least one cycle of FOLFIRINOX in this setting were evaluated for efficacy and toxicity.

Treatment

Standard FOLFIRINOX consisted of Oxaliplatin 85 mg/m² IV infused over 120 minutes, Irinotecan 180 mg/m² IV infused over 90 minutes, Folinic Acid 400 mg/m² IV infused over 30 minutes, 5-Fluorouracil 400 mg/m² IV in bolus infusion and 5-Fluorouracil 2,400 mg/m² IV in continuous infusion over 46 hours. Modified FOLFIRINOX consisted of Oxaliplatin 50–85 mg/m², Irinotecan 60–180 mg/m², Folinic Acid 0–400 mg/m², bolus 5-Fluorouracil 0–400 mg/m² and continuous infusion 5-Fluorouracil 1,800–2,400 mg/m². The same infusion protocols were used for standard and modified FOLFIRINOX and in both FOLFIRINOX protocols, cycles were repeated every 14 days. Patients who underwent at least one cycle of full-dose FOLFIRINOX constitute the standard FOLFIRINOX group. The remaining patients constitute the modified FOLFIRINOX group.

Patients routinely received Dexamethasone 10 mg IV and Ondansetron 12 mg IV immediately before the start of each cycle as chemotherapy-induced nausea and vomiting prophylaxis. Patients were oriented to use Ondansetron 8 mg PO every 8 hours afterwards up to the third day of

chemotherapy. According to the tolerance to chemotherapy, further escalation of anti-emetics was implemented. Atropine (0.5 mg) was administered before the infusion of Irinotecan in order to avoid acute cholinergic symptoms. In some patients, primary prophylaxis with G-CSF was performed at the discretion of the treating physician. This was accomplished by the use of Filgrastim 300 mcg SC for 2 to 6 days, or by a single subcutaneous injection of either pegfilgrastim or lipegfilgrastim (both 6 mg). G-CSF was started on the fourth day of the chemotherapy cycle.

Procedures

Data regarding response were extracted from original radiological reports and there was no independent radiological imaging review. Assessment of tumor response was performed every four to six cycles with multi-detector computer tomography (MD-CT) or magnetic resonance imaging (MRI) or both. Biochemical tumor response was described according to changes in tumor markers after the beginning of treatment. Such measurements took place every four to six cycles. Patients with baseline serum CA 19-9 ≤ 37 U/mL or baseline serum CEA ≤ 5 ng/mL were considered to have a normal tumor marker level. Baseline tumor markers were collected at the diagnosis of metastatic disease, regardless of the biliary tract patency.

Predictor variables

We collected data on baseline patients' characteristics: age, gender, ECOG performance status, Age-Adjusted Charlson Comorbidity Score (AACCS), body mass index (BMI), tumor site (head/neck *vs.* body/tail), number of metastatic sites, serum CA 19-9 at diagnosis of metastatic disease (U/mL), serum CEA at diagnosis of metastatic disease (ng/mL) and neutrophil-to-lymphocyte ratio (NLR) at diagnosis of metastatic disease. Patients for whom performance status was not available had their performance inferred from the description of patients' capabilities found in the medical records.

We also gathered information on the delivered treatment: dose (in mg/m²) of each drug in the first FOLFIRINOX cycle, number of cycles of FOLFIRINOX (total, before treatment de-escalation and after treatment de-escalation) and primary use of G-CSF. Additionally, we gleaned data on further lines of treatment. We assessed: the number of lines of treatment, percentage of patients treated in second- and third-line settings and the types of chemotherapy used in

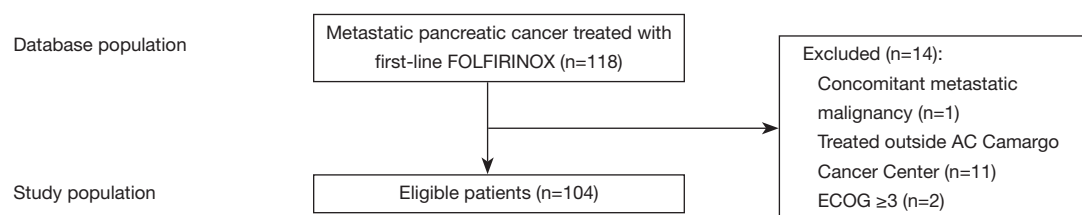
second- and third-line treatment.

Outcomes

The primary outcome of the study was overall survival (OS) according to treatment with either standard FOLFIRINOX or modified FOLFIRINOX. As secondary outcomes, we assessed differences in progression-free survival (PFS), biochemical response rates (for CA 19-9 and CEA), radiological tumor response rate and toxicity between these two groups. OS was defined as the time from the start of FOLFIRINOX to death (from any cause). Progression-free survival (PFS) was defined as the time from the start of FOLFIRINOX to death or disease progression (whatever took place first). Patients were censored at last follow-up visit in the absence of an event. We defined biochemical response as at least a 50% reduction in tumor marker level from baseline. Patients with normal levels of serum tumor markers at diagnosis were considered non-assessable for these analyses. Radiological tumor response was assessed using RECIST 1.1 criteria. Toxicity was graded according to the Common Toxicity Criteria version 4.0. Safety profile also included analysis of treatment delays (any delay), treatment de-escalations (withdrawal of either Oxaliplatin or Irinotecan or both), dose reductions (any dose reduction or withdrawal of bolus 5-Fluorouracil before treatment de-escalation), treatment-related mortality and severe toxicity (treatment-related complication mandating hospital admission). Toxicity was assessed not only in the first, but in all cycles of FOLFIRINOX.

Statistical analysis

We used absolute values and ratios to describe the distribution of categorical variables. Distributions of categorical variables were compared using Fisher's exact test. We used median values and the interquartile range (IQR) to describe the distribution of numerical variables. For chemotherapy dose at first cycle of FOLFIRINOX, we also used mean and standard deviation values. Distributions of numerical variables were compared using the Mann-Whitney test. We generated curves to describe time-to-event variables (OS and PFS) according to the Kaplan-Meier method. Survival curves were compared using the log-rank test. We used Cox's Proportional Hazard method to performed univariate analysis on OS and PFS. Variables with Wald's P value < 0.20 in univariate analysis were selected for multivariate analysis. As baseline NLR,

**Figure 1** Study population.**Table 1** Demographical and clinical features of the study population

Characteristic	Standard FOLFIRINOX (N=60)	Modified FOLFIRINOX (N=44)	P
Age (years)	56.0 [50.7–60.0]	62.0 [57.0–69.2]	<0.001
Sex			0.69
Male	33 (55.0)	22 (50.0)	
Female	27 (45.0)	22 (50.0)	
ECOG			0.40
0	29 (48.3)	16 (36.4)	
1	27 (45.0)	23 (52.3)	
2	4 (6.7)	5 (11.4)	
AACCS	7 [7–8]	8.5 [8–9]	<0.001
BMI (kg/m ²)	25.0 [21.1–27.8]	24.4 [21.9–27.8]	0.94
Tumor site			1.0
Head/neck	29 (48.3)	21 (47.8)	
Body/tail	31 (51.7)	23 (52.2)	
Number of metastatic sites	1 [1–2]	1 [1–2]	0.28
CA 19-9 (U/mL)	885.7 [93.9–6,414.7]	1,118.0 [87.2–8,173.5]	0.50
CEA (ng/mL)	8.8 [2.6–29.0]	15.0 [3.5–57.2]	0.42
Neutrophil-to-lymphocyte ratio	3.6 [2.4–4.8]	4.0 [3.1–5.2]	0.14

Data are shown as number (percentage) or median [IQR]. AACCS, Age-Adjusted Charlson Comorbidity Score.

serum CA 19-9 and serum CEA showed extremely right-skewed distributions, for didactic purposes, we transformed these variables to the logarithmic base (log₁₀) in the regression model. We considered two-tailed P values <0.05 as statistically significant. For the numerical variables independently associated with OS, we performed cut-off analysis based on the maximally selected rank statistics method (17). Statistical analysis was performed with the software R Project version 3.4.0 along with the survival and MaxStat packages.

Results

Through a search in the AC Camargo Cancer Center Pancreatic Cancer Database, we identified 118 patients treated for MPA with first-line FOLFIRINOX from January 1st 2010 through December 31th 2016 (*Figure 1*). Fourteen patients were excluded due to: ECOG 3 (2 patients), concomitant metastatic malignancy (1 patient) and treatment performed outside AC Camargo Cancer Center (11 patients). *Table 1* describes the characteristics of the study population. The median age was 59 years old

Table 2 Description of treatment details for the study population

Chemotherapy feature	Standard FOLFIRINOX (N=60)	Modified FOLFIRINOX (N=44)	P
Chemotherapy dose at 1 st cycle			
Oxaliplatin (mg)			0.04
Median (IQR)	84.8 (84.5–85.0)	84.6 (71.4–85.0)	
Mean (SD)	84.7 (2.8)	78.9 (9.0)	
Irinotecan (mg)			<0.001
Median (IQR)	179.6 (179.0–180.0)	150.0 (143.4–179.3)	
Mean (SD)	178.0 (8.2)	152.5 (25.2)	
5-Fluorouracil (bolus) (mg)			<0.001
Median (IQR)	399.8 (398.0–400.0)	0 (0–354.6)	
Mean (SD)	397.4 (13.3)	137.4 (185.1)	
5-Fluorouracil (infusion) (mg)			0.31
Median [IQR]	2,400 [2,389–2400]	2,400 [2,043–2,400]	
Mean (SD)	2,387 (81.4)	2,276 (207.3)	
Cycles of FOLFIRINOX			0.18
Median (IQR)	12.0 (7.5–18.2)	10.0 (4.0–16.0)	
Mean (SD)	13.6 (9.8)	12.2 (11.2)	
Cycles of FOLFIRINOX without de-escalation			0.86
Median (IQR)	8.5 (4–10.2)	6.5 (3.7–12.0)	
Mean (SD)	7.8 (4.7)	7.5 (4.8)	
Cycles of FOLFIRINOX with de-escalation			0.31
Median (IQR)	2 (0–8.2)	1 (0–5.5)	
Mean (SD)	5.7 (8.3)	4.7 (8.7)	
Primary prophylaxis/G-CSF, n (%)			0.31
Yes	33 (55.0)	29 (65.9)	
No	27 (45.0)	15 (34.1)	

G-CSF, granulocyte colony-stimulating factor.

(IQR, 52.7–65.0 years old). Most patients were male (52.9%, N=55). Only 8.7% of patients presented ECOG 2 and the median AACCs was 8 (IQR, 7–9). Most patients were eutrophic according to BMI status (median BMI =24.5; IQR, 21.3–27.8). Nearly half of the primary tumors were located in the pancreatic head/neck (48.1%, N=50) and most patients presented a single site of metastasis (median number of metastatic sites =1; IQR, 1–2). Median serum CA 19-9 at diagnosis was 1,114.7 U/mL (IQR, 90.3–6,549.0 U/mL), median serum CEA at diagnosis was 10.1 ng/mL (IQR, 2.9–47.4 ng/mL) and median NLR at diagnosis was 3.7 (IQR,

3.0–5.1). Comparing both treatment groups, patients treated with standard FOLFIRINOX were younger ($P<0.001$) and presented lower AACCs ($P<0.001$).

Treatment

Table 2 depicts treatment characteristics in the two groups. The standard FOLFIRINOX arm comprise 60 patients and 44 patients constitute the modified FOLFIRINOX arm. Two patients that initiated treatment with modified FOLFIRINOX and after one cycle had treatment

Table 3 Radiological and biochemical response to treatment

Variable (RECIST 1.1)	Standard FOLFIRINOX (N=60), n (%)	Modified FOLFIRINOX (N=40), n (%)	P
Objective response	9 (15.0)	10 (22.7)	0.07
Complete response	0 (0)	2 (4.5)	
Partial response	9 (15.0)	8 (18.2)	
Stable disease	32 (53.3)	16 (36.4)	
Progressive disease	12 (20.0)	6 (13.6)	
Not available	7 (11.7)	12 (27.3)	
CA 19-9 [§]			0.66
Response [#]	28 (46.7)	19 (43.2)	
No response	15 (25.0)	11 (25.0)	
Do not express CA 19-9	11 (18.3)	6 (13.6)	
Not available	6 (10.0)	8 (18.2)	
CEA [§]			0.55
Response [#]	16 (26.7)	14 (31.8)	
No response	11 (18.3)	8 (18.2)	
Do not express CEA	18 (30.0)	8 (18.2)	
Not available	15 (25.0)	14 (31.8)	

[§], normal CA 19-9 at staging defined as ≤ 37 U/mL; [§], normal CEA at staging defined as ≤ 5 ng/mL; [#], response defined as $\geq 50\%$ reduction from baseline.

escalation to full-dose FOLFIRINOX were included in the standard FOLFIRINOX group. During the first cycle of FOLFIRINOX, similar doses of continuous infusion 5-Fluorouracil were administered in both groups. Conversely, lower doses of Oxaliplatin, Irinotecan and bolus 5-Fluorouracil were given in the modified FOLFIRINOX group. Also, there was no difference in the total number cycles of FOLFIRINOX delivered, as well as in the number of FOLFIRINOX cycles before or after treatment de-escalation.

Efficacy

Table 3 illustrates the radiological and biochemical responses to treatment. There were no differences in serum CEA and serum CA 19-9 changes in response to treatment between the two treatment arms. The objective response rate was numerically higher in patients treated with modified FOLFIRINOX (standard FOLFIRINOX =15.0% *vs.* modified FOLFIRINOX =22.7%), but this difference was not statistically significant ($P=0.07$). After excluding

patients not expressing a specific tumor marker and those not assessed for biochemical response, statistically significant associations were seen between CEA response ($N=40$; Fisher exact test $P=0.03$) and radiological response to chemotherapy and between CA 19-9 response ($N=65$; Fisher exact test $P=0.001$) and radiological response to chemotherapy.

Median follow-up time was 28.6 months (95% CI 20.8–NA). At last follow-up, 49 patients in the standard FOLFIRINOX arm were dead and 27 patients in the modified FOLFIRINOX arm were dead. No difference in OS was detected between the two treatment groups. Median overall survival was 13.4 months in the standard FOLFIRINOX arm and 12.1 months in modified FOLFIRINOX arm (HR =0.86; 95% CI, 0.53–1.38; $P=0.54$; Figure 2). One- and two-year OS rates were 56.4% and 19.3% in the standard FOLFIRINOX group and 54.8% and 22.2% in the modified FOLFIRINOX group, respectively. In the multivariate model, no difference in overall survival was detected between the two treatment arms (HR =0.94; 95% CI, 0.51–1.72; $P=0.84$; Table 4). At

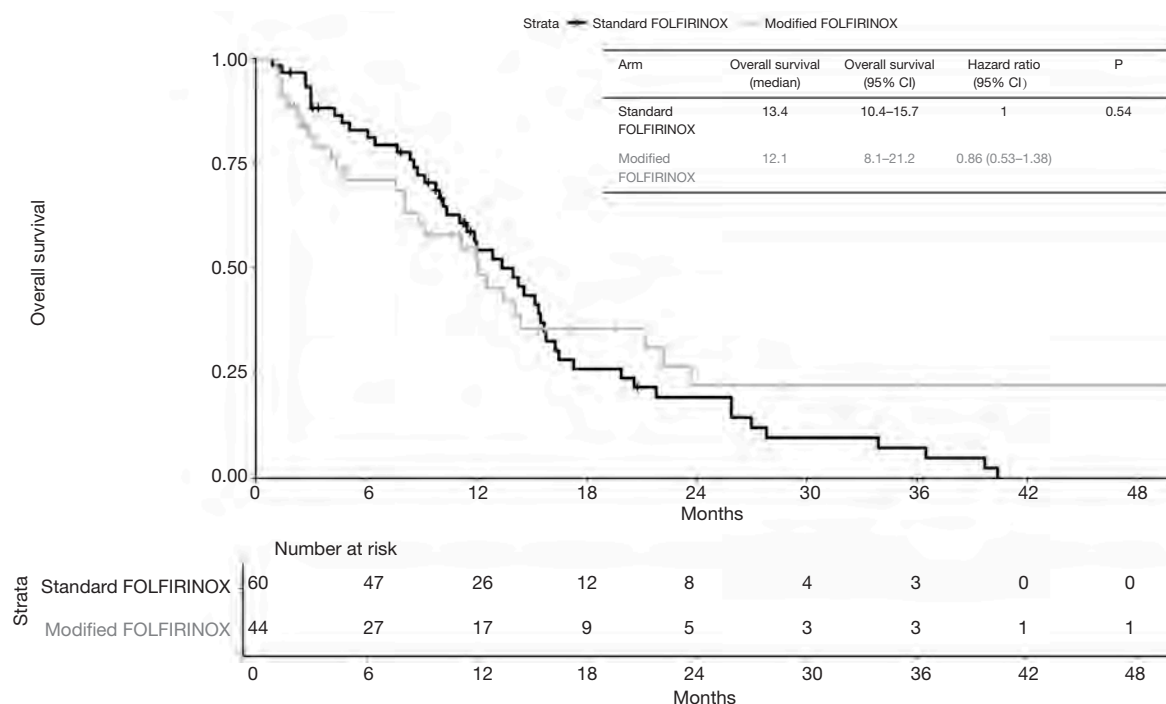


Figure 2 Overall survival of patients treated with standard FOLFIRINOX and with modified FOLFIRINOX.

last follow-up, 56 patients were dead or experienced disease progression in the standard FOLFIRINOX arm and 38 patients were dead or experienced disease progression in the modified FOLFIRINOX arm. No difference in progression-free survival was detected between the two treatment arms. Median progression-free survival was 8.9 months in the standard FOLFIRINOX arm and 8.1 months in the modified FOLFIRINOX arm (HR =0.95; 95% CI, 0.62–1.44; P=0.81; *Figure 3*). One- and 2-year PFS rates were 18.0% and 2.0% in the standard FOLFIRINOX group and 23.1% and 12.8% in the modified FOLFIRINOX group, respectively. In the multivariate model, no difference in progression-free survival was detected between the two treatment arms (HR =1.13; 95% CI, 0.65–1.96; P=0.66; *Table 5*).

Prognostic factors

Tables 4,5 describe the prognostic factors for OS and PFS, respectively. In the multivariate analysis, only log₁₀(NLR) was independently associated with OS (HR =3.60; 95% CI, 1.28–10.10; P=0.01). In turn, the number of metastatic sites (HR =1.32; 95% CI, 1.02–1.70; P=0.03), log₁₀(CA 19-9) (HR =1.26; 95% CI, 1.01–1.58; P=0.03) and

log₁₀(NLR) (HR =5.22; 95% CI, 1.84–14.76; P=0.001) were independent predictors of PFS. Cut-off analysis revealed 5.2 represented the best NLR threshold for OS. After dichotomizing neutrophil/lymphocyte ratio (≤ 5.2 vs. >5.2), significant differences in OS (HR =2.74; 95% CI, 1.54–4.87; P<0.001) and PFS (HR =2.58; 95% CI, 1.52–4.37; P<0.001) were observed. Also, after excluding patients not assessable for tumor response, response to treatment according to RECIST (complete or partial response) was related to better OS (HR =0.42; 95% CI, 0.22–0.79; P=0.007) and PFS (HR =0.44; 95% CI, 0.25–0.76; P=0.003) in comparison to patients experiencing stable or progressive disease.

Toxicity

Table 6 illustrates the toxicity profiles of standard and modified FOLFIRINOX. Overall, there were no major differences in toxicity between the two treatment arms. Slightly higher rates of grades 3 or 4 constipation (0% vs. 4.5%) and leukopenia (1.7% vs. 9.1%) were seen in patients in the modified FOLFIRINOX group. In turn, mildly increased incidence of fatigue was seen in patients treated with standard FOLFIRINOX (6.8% vs. 2.3%).

Table 4 Prognostic factors for overall survival

Characteristic	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age	0.97	0.95–1.00	0.14	0.97	0.94–1.01	0.21
Sex						
Male	1					
Female	1.26	0.80–1.99	0.30			
ECOG						
0	1					
1	1.38	0.86–2.22	0.17			
2	0.81	0.28–2.29	0.69			
AACCS	0.89	0.73–1.09	0.28			
BMI	1.00	0.95–1.05	0.89			
Tumor site						
Head/neck	1					
Body/tail	0.96	0.61–1.51	0.86			
Number of metastatic sites	1.27	0.99–1.64	0.05	1.20	0.87–1.66	0.26
Log ₁₀ (CA 19-9)	1.25	1.03–1.53	0.02	1.13	0.89–1.43	0.30
Log ₁₀ (CEA)	1.35	1.03–1.78	0.02	1.12	0.82–1.54	0.44
Log ₁₀ (neutrophil-to-lymphocyte ratio)	2.75	1.16–6.53	0.02	3.60	1.28–10.10	0.01
Modified FOLFIRINOX						
No	1					
Yes	0.86	0.53–1.38	0.54	0.94	0.51–1.72	0.84

Also, chemotherapy dose reductions were more common in the standard FOLFIRINOX arm (40.0% *vs.* 31.8%). Conversely, toxicities mandating hospitalization (18.6% *vs.* 31.8%) and treatment-related mortality (0.0% *vs.* 4.5%) were more frequent in the modified FOLFIRINOX arm. None of these differences were statistically significant. Two patients died as a consequence of the treatment. In the modified FOLFIRINOX arm, one patient died as a consequence of sinonasal mucormycosis and another patient died of febrile neutropenia/intraabdominal infection.

Further treatment

Table 7 describes therapy beyond first-line in both treatment arms. Patients in the standard FOLFIRINOX arm were more prone to receive second- (P=0.007) and

third-line treatments (P=0.06). Overall, the median number of treatment lines also was higher in the standard FOLFIRINOX arm (P=0.002). Gemcitabine based-chemotherapy regimens were among the most commonly used therapies both in second- and in third-line.

Discussion

Data from randomized clinical trials have established FOLFIRINOX as one of the standard treatment regimens for patients with MPA. Nonetheless, it has been primarily tested in patients relatively young and with good performance status. Even in this selected group, high rates of toxicity, namely neutropenia, have been described. As a consequence, modifications of this regimen have been tested to improve the toxicity profile of FOLFIRINOX.

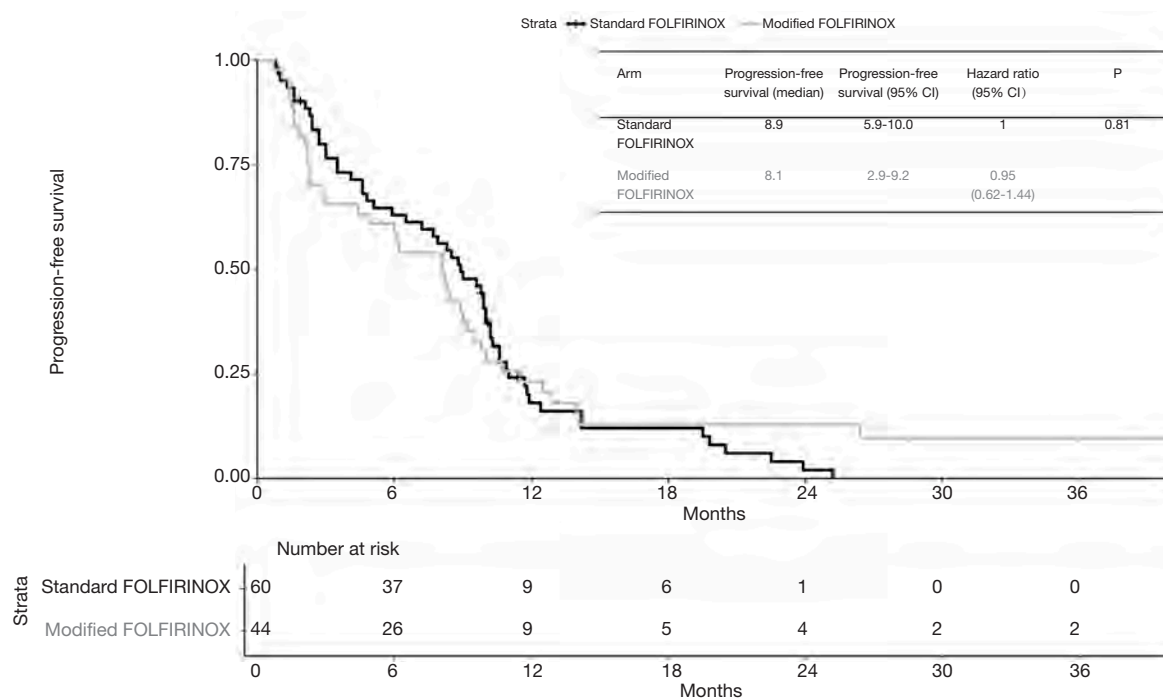


Figure 3 Progression-free survival of patients treated with standard FOLFIRINOX and with modified FOLFIRINOX.

In this study, we detected no differences in PFS or OS between patients treated with standard FOLFIRINOX or with modified FOLFIRINOX. Also, we demonstrated that reductions in the FOLFIRINOX dose had no impact in the response according to tumor marker kinetics or RECIST.

Our survival data are in line with other investigations evaluating the role of modified FOLFIRINOX in patients with MPA. The first prospective trial of modified FOLFIRINOX in MPA was published by Stein *et al.* (12). They enrolled 31 patients with locally advanced pancreatic adenocarcinoma and 37 patients with MPA to treatment with attenuated doses of FOLFIRINOX (Irinotecan 135 mg/m² and bolus 5-Fluorouracil 300 mg/m²). The response rate was 35.1% in the cohort of patients with metastatic disease. Median PFS and median OS in this group were 6.1 and 10.2 months, respectively. Ueno *et al.* undertook a phase 2 study evaluating the activity of a modified FOLFIRINOX regimen (Irinotecan 150 mg/m² and no 5-Fluorouracil bolus) in 69 patients with metastatic pancreatic cancer (13). The objective response rate was 37.7%. Median PFS and median OS were 5.5 and 11.2 months, respectively. Similarly, Li *et al.* conducted a phase 2 trial exclusively in patients with MPA testing a modified FOLFIRINOX regimen with reduced doses of both Oxaliplatin (85% of

standard dose) and Irinotecan (75% of standard dose), along with the omission of bolus 5-Fluorouracil (14). Among the 62 eligible patients, the overall response rate was 32.5%. Median PFS and median OS were 7.0 and 10.3 months, respectively. These outcomes are similar to the ones found in the ACCORD 11/PRODIGE 4 study. In this study, the overall response rate was 31.6%; median PFS and median OS were 6.8 and 11.1 months, respectively. Additionally, a retrospective Canadian study have shown similar survival for patients with MPA treated with standard or modified FOLFIRINOX regimens (7). Taken together, this data point to a similar activity of modified FOLFIRINOX as compared do standard FOLFIRINOX.

Despite the evidence in favor of modified FOLFIRINOX, the proper doses of the different agents in this regimen are still a source of argument, as a variety of doses have been used. Recent data point the doses of the different drugs used in FOLFIRINOX must be significantly reduced before a loss of effectiveness is observed. Decreased response rate and disease control rate have been show to occur only after the median dose intensity of FOLFIRINOX is reduced to less than 70% and 55%, respectively (18). In our study, dose reductions were left to discretion of the treating physician. As a result, different modified FOLFIRINOX regimens

Table 5 Prognostic factors for progression-free survival

Characteristic	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age	0.98	0.96–1.00	0.17	0.97	0.92–1.02	0.32
Sex						
Male	1					
Female	1.24	0.82–1.87	0.29			
ECOG						
0	1			1		
1	1.43	0.94–2.19	0.08	0.98	0.59–1.63	0.96
2	0.58	0.23–1.49	0.26	0.36	0.12–1.11	0.07
AACCS	0.88	0.74–1.06	0.19	1.04	0.72–1.49	0.82
BMI	1.00	0.96–1.05	0.79			
Tumor site						
Head/neck	1					
Body/tail	1.14	0.75–1.71	0.52			
Number of metastatic sites	1.34	1.09–1.65	0.004	1.32	1.02–1.70	0.03
Log ₁₀ (CA 19-9)	1.29	1.07–1.55	0.005	1.26	1.01–1.58	0.03
Log ₁₀ (CEA)	1.18	0.93–1.48	0.15	0.86	0.66–1.13	0.29
Log ₁₀ (neutrophil-to-lymphocyte ratio)	1.94	0.96–3.92	0.06	5.22	1.84–14.76	0.001
Modified FOLFIRINOX						
No	1					
Yes	0.95	0.62–1.44	0.81	1.13	0.65–1.96	0.66

were used. In most cases, the doses of Oxaliplatin and continuous infusion 5-Fluorouracil were maintained. The relevant differences lied on the doses of bolus 5-Fluorouracil and Irinotecan. Most of the patients treated with modified FOLFIRINOX had bolus 5-Fluorouracil omitted. This is similar to what has been reported in prospective (13,14) and retrospective studies of modified FOLFIRINOX in pancreatic cancer (16,19,20). In colorectal cancer, the omission of bolus 5-Fluorouracil has shown to improve the toxicity profile while maintaining treatment activity (21,22). Even in anatomical borderline pancreatic adenocarcinoma, a setting in which optimization of response is pursued in order to achieve R0 resections, FOLFIRINOX has been recently employed without bolus 5-Fluorouracil (23). Thus, these arguments speak in favor of omitting bolus 5-Fluorouracil from FOLFIRINOX in patients with MPA.

In our study, the mean dose and the median dose of

Irinotecan in the first cycle of modified FOLFIRINOX were 152.5 and 150 mg/m², respectively. In previous investigations, modified FOLFIRINOX regimens usually had decreased doses of Irinotecan, ranging from 135 to 165 mg/m² (12–14,16,19,24). Irinotecan adds significantly to the occurrence of nausea, vomiting and diarrhea when used in triplet-chemotherapy regimens. In patients treated with FOLFOXIRI, a regimen with a decrease in the dose of Irinotecan to 165 mg/m², the frequency of grade 3–4 vomiting (3.6%) is significantly lower than that found in the ACCORD 11/PRODIGE 4 trial (14.5%) with standard FOLFIRINOX (25). Also, reduced activity of UGT1A have been detected in a significant proportion of the population and individuals carrying this enzymatic deficiency are at increased risk for severe toxicity when treated with Irinotecan (26,27). In Brazil, routine testing for UGT1A deficiency is not available before starting Irinotecan, and we

Table 6 Toxicity profile of standard and modified FOLFIRINOX

Event	Toxicity, n (%)		P
	Standard FOLFIRINOX [§] (N=59)	Modified FOLFIRINOX (N=44)	
Any G3–4 toxicity	21 (35.6)	16 (36.4)	1.00
Non-hematologic toxicity			
Nausea	2 (3.4)	1 (2.3)	1.00
Vomiting	2 (3.4)	1 (2.3)	1.00
Constipation	0 (0.0)	2 (4.5)	0.18
Diarrhea	1 (1.7)	2 (4.5)	0.57
Mucositis	2 (3.6)	1 (2.3)	1.00
Fatigue	4 (6.8)	1 (2.3)	0.38
Decreased appetite	1 (1.7)	0 (0.0)	1.00
Peripheral neuropathy	4 (6.9)	2 (4.5)	1.00
Hematologic toxicity			
Anemia	3 (5.1)	3 (6.8)	1.00
Leukopenia	1 (1.7)	4 (9.1)	0.16
Neutropenia	9 (15.3)	7 (15.9)	1.00
Thrombocytopenia	4 (6.8)	5 (11.4)	0.49
Febrile neutropenia	2 (3.4)	3 (6.8)	0.64
Treatment delay	27 (45.8)	21 (47.7)	1.00
Dose reduction	24 (40.0)	14 (31.8)	0.41
Severe toxicity	11 (18.6)	14 (31.8)	0.16
Treatment mortality	0 (0.0)	2 (4.5)	0.18

[§], data on toxicity was not available for one patient submitted to treatment with standard FOLFIRINOX.

believe by starting FOLFIRINOX with decreased doses of Irinotecan in these patients we may lower the risk of severe toxicities (namely neutropenia and diarrhea) that occur in the first few cycles of treatment (9). As a result, dose reductions in Irinotecan can be employed in the first cycle and we consider 150 mg/m² a reasonable dosing choice in this setting.

The overall response rate observed in our study is somewhat lower than previously described (4,6,12). That may be explained by the lack of independent radiological review. Also, some studies describe response rates only for the assessable patients (7,28). Had we done that, our response rate would be 31.2% and 16.9% for modified and standard FOLFIRINOX, respectively. These figures approach the response rate observed in clinical trials using FOLFIRINOX in MPA (4,6,12). However, we believe that

many patients not assessable for tumor response experience early treatment failure or significant treatment toxicity, demonstrating a lack of treatment benefit. Despite the lower response seen in our study, there was a strong correlation between response according to RECIST and response according to CA 19-9 or CEA kinetics. Additionally, patients experiencing objective response to FOLFIRINOX showed markedly improved PFS and OS.

One of the main arguments in favor of a modification of FOLFIRINOX is a potential decrease in treatment toxicity. In our study, we were not able to demonstrate significant improvements in the toxicity profile with modified FOLFIRINOX when compared to standard FOLFIRINOX. Severe toxicities were relatively uncommon in our population. We acknowledge this may stem from the retrospective nature of our study. In addition, patients

Table 7 Further systemic treatment after FOLFIRINOX

Treatment feature	Standard FOLFIRINOX (N=60)	Modified FOLFIRINOX (N=44)	P
Second-line chemotherapy	45 (75.0)	21 (47.7)	0.007
Gemcitabine	22 (36.6)	5 (11.3)	
Gemcitabine + platinum	3 (5.0)	6 (13.6)	
Gemcitabine + taxane	4 (6.7)	2 (4.5)	
FOLFOX	10 (16.7)	3 (6.8)	
FOLFIRI	5 (8.3)	1 (2.2)	
FOLFIRINOX	0 (0.0)	4 (9.0)	
Others	1 (1.7)	0 (0.0)	
Third-line chemotherapy	20 (33.3)	7 (15.9)	0.06
Gemcitabine	6 (10.0)	0 (0.0)	
Gemcitabine + platinum	1 (1.7)	1 (2.2)	
Gemcitabine + taxane	2 (3.3)	0 (0.0)	
FOLFOX	3 (5.0)	1 (2.2)	
FOLFIRI	4 (6.7)	2 (4.5)	
FOLFIRINOX	1 (1.7)	0 (0.0)	
Taxane	1 (1.7)	2 (4.5)	
Others	2 (3.3)	1 (2.2)	
Number of lines of chemotherapy	2 [1.75–3]	1 [1–2]	0.002

Data are shown as number (percentage) and median [IQR].

treated with modified FOLFIRINOX were less fit than those treated with standard FOLFIRINOX. They were older and presented more comorbidities according to the Age-Adjusted Charlson Comorbidity Score (AACCS). Moreover, they were also less likely to undergo further systemic treatments after progression on FOLFIRINOX. Thus, we believe the use of decreased doses of chemotherapy might have minimized the risk of complications in this group of patients. Also, the use of prophylactic G-CSF may have biased the toxicity analysis. Most of our patients had primary febrile neutropenia prophylaxis. The rates of grade 3–4 neutropenia in both groups were much lower than described in the ACCORD 11/PRODIGE 4 trial. Had that not been the case, we believe the rates of severe toxicity in the standard FOLFIRINOX would have been higher, since complications such as febrile neutropenia commonly occur in the first few cycles during treatment with FOLFIRINOX. As a result, further studies must be undertaken to evaluate the role of prophylactic G-CSF in lowering hematological toxicity during treatment with FOLFIRINOX.

In our study, NLR proved to be the most important predictor of outcome. Moreover, patients with NLR >5.2 presented the highest risk for early death. That is not specific for FOLFIRINOX, as similar data have also been reported for Gemcitabine + Nab-paclitaxel (29,30) and FOLFOXIRI (25). Also, the threshold for NLR found in our study matches the ones found in the literature (31). It is not clear from recent data if the NLR is only a marker of systemic inflammation or if the increased neutrophils have an independent biological meaning. Recent data point neutrophils may facilitate the occurrence of metastatic disease by means of direct interactions with circulating pancreatic cancer cells (32). Nonetheless, increased numbers of peripheral neutrophils may simply reflect higher concentrations of inflammatory cytokines, such as G-CSF. Recently, it has been demonstrated in a murine model that elevated tumor levels of G-CSF correlate with an aggressive tumor phenotype (33). This phenotype seems to be primarily driven by the immune-suppressive properties of G-CSF, and could be abrogated by treatment with an antibody directed

against G-CSF. As a result, we believe additional work is needed to better understand the relation between NLR and the cytokine milieu in patients with MPA.

Our study presents some limitations. We acknowledge that as a single center retrospective study, bias may have played a role in the results. Also, we were not able to obtain independent radiology imaging review and serum CA 19-9 levels were analyzed in the presence of cholestasis in some patients. We also could not collect data on dose intensity beyond the first cycle of FOLFIRINOX. Nevertheless, we believe that the choice of the dose in the first cycle carries more practical implications than overall treatment dose intensity, as dose reductions are dictated not by intended dose-intensity, but by the presenting toxicity. Also, some of the most serious adverse events from FOLFIRINOX treatment frequently take place after the first cycle (9), emphasizing the need for careful dose selection for the first cycle. Moreover, this is one of the largest studies evaluating the role of modified FOLFIRINOX in pancreatic cancer. We analyzed its activity in a population comprised exclusively of patients with metastatic disease and treated in the same hospital, with access to similar support and medical expertise. Our survival results match those of studies previously published. In addition, we found significant associations between NLR and outcomes, with a threshold similar to those already described.

To conclude, modified FOLFIRINOX demonstrated similar activity to that of standard FOLFIRINOX in patients with MPA. No major differences in toxicity were observed, mainly due to selection bias, uneven dose reductions and unrestricted use of prophylactic G-CSF. Prognosis for patients with an elevated NLR is poor, and efforts should be concerted to better comprehend the biological mechanisms behind this phenomenon in order to improve treatment outcomes.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the AC

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References

1. Golan T, Sela T, Margalit O, et al. Short and long-term survival in metastatic pancreatic adenocarcinoma, 1993–2013. *J Natl Compr Canc Netw* 2017;15:1022–7.
2. Sirri E, Castro FA, Kieschke J, et al. Recent Trends in Survival of Patients with Pancreatic Cancer in Germany and the United States. *Pancreas* 2016;45:908–14.
3. Von Hoff DD, Ervin T, Arena FP, et al. Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine. *N Engl J Med* 2013;369:1691–703.
4. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817–25.
5. Gourgu-Bourgade S, Bascoul-Mollevis C, Desseigne F, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: Results from the PRODIGE 4/ACCORD 11 randomized trial. *J Clin Oncol* 2013;31:23–9.
6. Singhal M, Kapoor A, Bagri P. A phase III trial comparing FOLFIRINOX versus Gemcitabine for metastatic pancreatic cancer. *Ann Oncol* 2014;25:iv210–53.
7. Chhanna MK, Cook N, Dhani NC, et al. FOLFIRINOX for advanced pancreatic cancer: The Princess Margaret Cancer Centre experience. *Br J Cancer* 2016;115:649–54.
8. Metges J, Ramée J, Douillard JY, et al. Efficacy and safety of FOLFIRINOX in patients with metastatic pancreatic cancer. *J Clin Oncol* 2014;32:abstr 305.
9. Okusaka T, Ikeda M, Fukutomi A, et al. Phase II study of FOLFIRINOX for chemotherapy-naïve Japanese patients with metastatic pancreatic cancer. *Cancer Sci* 2014;105:1321–6.
10. Weycker D, Li X, Edelsberg J, et al. Risk of febrile neutropenia in patients receiving emerging chemotherapy regimens. *Support Care Cancer* 2014;22:3275–85.
11. Patel L, Hollmann S, Attard C, et al. Real-world experience with FOLFIRINOX: A review of Canadian and international registries. *Oncol Exch* 2014;13:18–23.
12. Stein SM, James ES, Deng Y, et al. Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer. *Br J Cancer* 2016;114:737–43.
13. Ueno M, Ozaka M, Ishii H, et al. Phase II study of modified FOLFIRINOX for chemotherapy-naïve

- patients with metastatic pancreatic cancer. *J Clin Oncol* 2016;34:abstr 4111.
14. Li X, Ma T, Zhang Q, et al. Modified-FOLFIRINOX in metastatic pancreatic cancer: A prospective study in Chinese population. *Cancer Lett* 2017;406:22-6.
 15. Gunturu K, Thumar J, Hochster H, et. Single-institution experience with FOLFIRINOX in advanced pancreatic cancer (PC). *J Clin Oncol* 2012;30:abstr 330.
 16. Mahaseth H, Brucher E, Kauh J, et al. Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. *Pancreas* 2013;42:1311-5.
 17. Lausen B, Schumacher M. Maximally Selected Rank Statistics. *Biometrics* 1992;48:73-85.
 18. Lee JC, Kim JW, Ahn S, et al. Optimal dose reduction of FOLFIRINOX for preserving tumour response in advanced pancreatic cancer: Using cumulative relative dose intensity. *Eur J Cancer* 2017;76:125-33.
 19. Blazer M, Wu CS, Goldberg R, et al. Tolerability and efficacy of modified FOLFIRINOX (mFOLFIRINOX) in patients with borderline-resectable pancreatic cancer (BRPC) and locally advanced unresectable pancreatic cancer (LAURPC). *J Clin Oncol* 2014;32:abstr 275.
 20. Alessandretti M, Moreira R, Brandao E, et al. Safety and efficacy of modified dose- attenuated FOLFIRINOX chemotherapy in patients over 65 years with advanced pancreatic adenocarcinoma. *J Clin Oncol* 2015;33:abstr 468.
 21. Denda T, Kanda M, Morita Y, et al. Pharmacokinetic dose adjustment of 5-FU in modified FOLFOX7 plus bevacizumab for metastatic colorectal cancer in Japanese patients: a-JUST phase II clinical trial. *Cancer Chemother Pharmacol* 2016;78:1253-61.
 22. Tezuka T, Hamada C, Ishida H, et al. Phase II clinical study of modified FOLFOX7 (intermittent oxaliplatin administration) plus bevacizumab in patients with unresectable metastatic colorectal cancer—CRAFT study. *Invest New Drugs* 2013;31:1321-9.
 23. Katz MH, Shi Q, Ahmad SA, et al. Preoperative Modified FOLFIRINOX Treatment Followed by Capecitabine-Based Chemoradiation for Borderline Resectable Pancreatic Cancer: Alliance for Clinical Trials in Oncology Trial A021101. *JAMA Surg* 2016;151:e161137.
 24. Ghorani E, Wong HH, Hewitt C, et al. Safety and Efficacy of Modified FOLFIRINOX for Advanced Pancreatic Adenocarcinoma: A UK Single-Centre Experience. *Oncology* 2015;89:281-7.
 25. Vivaldi C, Caparello C, Musettini G, et al. First-line treatment with FOLFOXIRI for advanced pancreatic cancer in clinical practice: Patients' outcome and analysis of prognostic factors. *Int J Cancer* 2016;139:938-45.
 26. Stingl JC, Bartels H, Viviani R, et al. Relevance of UDP-glucuronosyltransferase polymorphisms for drug dosing: A quantitative systematic review. *Pharmacol Ther* 2014;141:92-116.
 27. Rouits E, Boisdron-Celle M, Dumont A, et al. Relevance of different UGT1A1 polymorphisms in irinotecan-induced toxicity: A molecular and clinical study of 75 patients. *Clin Cancer Res* 2004;10:5151-9.
 28. Peddi PF, Lubner S, McWilliams R, et al. Multi-Institutional Experience with FOLFIRINOX in Pancreatic Adenocarcinoma. *JOP* 2012;13:497-501.
 29. Goldstein D, El-Maraghi RH, Hammel P, et al. Nab-paclitaxel plus gemcitabine for metastatic pancreatic cancer: Long-term survival from a phase III trial. *J Natl Cancer Inst* 2015;107:1-10.
 30. Ventriglia J, Alvaro M, Laterza M, et al. Final results of neutrophil-to-lymphocyte ratio (NLR) as a prognostic marker in advanced pancreatic cancer patients treated with Nab-paclitaxel plus Gemcitabine. *J Clin Oncol* 2016;34:abstr e15737.
 31. Piciucchi M, Stigliano S, Archibugi L, et al. The neutrophil/lymphocyte ratio at diagnosis is significantly associated with survival in metastatic pancreatic cancer patients. *Int J Mol Sci* 2017;18:3-11.
 32. Tao L, Zhang L, Peng Y, et al. Neutrophils assist the metastasis of circulating tumor cells in pancreatic ductal adenocarcinoma. *Medicine (Baltimore)* 2016;95:e4932.
 33. Pickup MW, Owens P, Gorska AE, et al. Development of aggressive pancreatic ductal adenocarcinomas depends on granulocyte-colony stimulating factor secretion in carcinoma cells. *Cancer Immunol Res* 2017;5:718-29.

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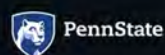
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Appendix GHORANI02

Safety and Efficacy of Modified FOLFIRINOX for Advanced Pancreatic Adenocarcinoma: A UK Single-Centre Experience

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Key Words

Pancreatic adenocarcinoma · Chemotherapy · FOLFIRINOX · Safety

Abstract

Objectives: The combination of 5-fluorouracil (5-FU), irinotecan and oxaliplatin (FOLFIRINOX) is considered the first-line chemotherapy for fit patients with advanced pancreatic ductal adenocarcinoma (PDAC) but carries an unfavourable adverse event (AE) profile. We retrospectively evaluated the tolerability and efficacy of a modified FOLFIRINOX (mFOLFIRINOX) regimen: intravenous oxaliplatin 85 mg/m², irinotecan 135 mg/m², folinic acid 400 mg/m² and 5-FU infusion 2,400 mg/m² over 46 h, with routine subcutaneous filgrastim on a 14-day cycle. **Methods:** Records of 18 patients with advanced PDAC who received treatment with mFOLFIRINOX were reviewed. Imaging of measurable disease was assessed for response, and survival was measured from the date of commencing chemotherapy to disease progression and/or death. **Results:** Grade 3 or 4 AEs (n; %) included vomiting (5; 28), nausea (4; 22), diarrhoea (3; 17) and

non-neutropaenic fever (3; 17). For patients with stage IV disease, 12/15 (80%) achieved at least stable disease as the best radiological response, with 7/15 (47%) objective responses. In this subgroup, median overall and progression-free survival were 9.3 months (95% CI 8.3–10.4) and 7.2 months (95% CI 4.7–9.6), respectively. **Conclusion:** Compared to full-dose FOLFIRINOX, our modified regimen resulted in lower haematological but only marginally improved non-haematological toxicity rates, with comparable efficacy outcomes. Prospective studies are required to validate these findings.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth most common cause of cancer-related death in Europe [1] with a 5-year survival rate of 6.9%, the lowest among the 46 most common cancers [2]. The majority of patients have unresectable disease at presentation, and palliative chemotherapy is offered to those patients fit enough to tolerate treatment. Until recently, single-agent

gemcitabine was the international standard of care. In 2011, Conroy et al. [3] reported a clinically significant benefit with the combination of 5-fluorouracil (5-FU), folinic acid, irinotecan and oxaliplatin (FOLFIRINOX) compared to gemcitabine, with a significant median overall survival (OS) advantage of 11.1 versus 6.8 months in patients with stage IV PDAC. Since then, FOLFIRINOX has been adopted as standard first-line combination chemotherapy for PDAC patients with very good performance status [Eastern Cooperative Oncology Group (ECOG) 0 or 1]. The survival gain comes at a cost, as FOLFIRINOX is associated with an unfavourable side effect profile, with significantly more grade 3 and 4 neutropenia (45.7 vs. 21.0%), diarrhoea (12.7 vs. 1.8%) and sensory neuropathy (9.0 vs. 0%) compared to gemcitabine. At full dose, therefore, tolerability remains a concern which has limited the routine use of FOLFIRINOX [4].

Recently, data from retrospective studies have suggested that modifications to the FOLFIRINOX regimen may decrease toxicities without compromising efficacy [5, 6], and a number of studies specifically investigating modified FOLFIRINOX (mFOLFIRINOX) regimens have subsequently been reported in abstract, providing some support for the hypothesis [7, 8]. In the only published study to date evaluating palliative mFOLFIRINOX in advanced pancreatic cancer patients, Mahaseh et al. [9] used a regimen which omitted the bolus 5-FU and incorporated routine haematopoietic growth factor support. The median OS of 60 treated patients was similar to that of the patients treated with the full-dose regimen (9.0 vs. 11.1 months), but in contrast to earlier reports [5, 6], suggesting a much improved toxicity profile with dose attenuation (e.g. <5% incidence of grade 3 and 4 diarrhoea, frequency of grade 3 and 4 non-haematological toxicities of diarrhoea (13%) and nausea was comparable, although fatigue was less common (summarised in table 6). In a recent retrospective neoadjuvant study, Blazer et al. [10] delivered a similar mFOLFIRINOX regimen with a slightly lower irinotecan dose of 160 mg/m², representing an approximately 10% dose reduction. This study also found rates of grade 3 and 4 diarrhoea similar to the full-dose regimen. Further data questioning the value of dose-attenuated FOLFIRINOX in limiting gastrointestinal toxicities have recently been presented by Lee et al. [11] who retrospectively reviewed the outcomes of 27 patients with advanced pancreatic adenocarcinoma, stratified by relative dose intensity (RDI). In this study, there was no significant difference in rates of grade 3/4 diarrhoea and nausea (25 vs. 29%) in the highest and lowest RDI groups (≥80 vs. 50–69%, respectively).

Questions about tolerability therefore remain relevant despite the prospect of comparable efficacy with dose attenuation. At our academic UK institution, we have routinely modified FOLFIRINOX by omitting the bolus dose of 5-FU, reducing irinotecan to 75% of the full dose and including routine haematopoietic growth factor support. We report here the results of a retrospective review of the safety and efficacy of mFOLFIRINOX in advanced pancreatic cancer patients.

Methods

Patient Selection and Treatment

A consecutive cohort of patients with advanced pancreatic adenocarcinoma treated with FOLFIRINOX between July 2011 and May 2014 at Cambridge University Hospitals NHS Foundation Trust (CUH) were identified, and those initiated on or converted to a modified regimen from cycle 2 were eligible for inclusion.

The intended treatment regimen consisted of oxaliplatin 85 mg/m², irinotecan 130–135 mg/m² (72–75% of the full dose), folinic acid 400 mg/m² and 5-FU infusion 2,400 mg/m² over 46 h administered every 14 days. All patients received haematopoietic growth factor support with filgrastim for 7 days with each cycle. Anti-emetic support with ondansetron 8 mg and dexamethasone 8 mg was routinely administered on day 1 of each cycle, and domperidone, ondansetron or aprepitant was prescribed for subsequent days at the discretion of the treating physician. Patients were provided loperamide and instructed to commence this at the onset of diarrhoea.

Treatment toxicities and subsequent dose adjustments were determined following clinical and laboratory evaluation at the beginning of each cycle. Baseline computed tomography (CT) staging was performed within 4 weeks of commencing chemotherapy. Reassessment CT scans were planned for after every four to six cycles. Treatment was discontinued in cases of disease progression or unacceptable toxicity.

Data Analysis

Patient data were collected from review of electronic medical records and paper case notes. Chemotherapy dose intensities were calculated according to the method of Hryniuk and Bush [12]. Toxicities were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. CT scans were reviewed and treatment response assessed as per Response Evaluation Criteria in Solid Tumours (RECIST). Progression-free survival (PFS) and OS were measured as the interval between the day of first treatment and documented radiological or clinical evidence of disease progression, and death, respectively. Data collection was terminated on the July 23, 2014, at which point patients who were alive and/or progression-free were censored for analysis.

Data analysis was on an intention-to-treat basis and carried out using Microsoft Excel and SPSS. Survival analysis was calculated using Kaplan-Meier estimators and adverse event (AE) rates were compared with historical data using Fisher's exact test.

Results

Patient Characteristics

Eighteen patients with advanced PDAC were treated with mFOLFIRINOX between July 2011 and May 2014 (table 1). The majority of patients had stage IV disease ($n = 15$, 83.3%) and tumours localised to the head of the pancreas ($n = 10$, 56.6%) with a median age of 60 years (range 40–77); all had ECOG performance status of 0 or 1.

Treatments

A median of 8.5 chemotherapy cycles was delivered (range 1–12), with median RDI calculated for 16 patients who received more than one cycle (table 2) as follows: 5-FU (83%), oxaliplatin (80%) and irinotecan (64%). A median of two cycles was achieved before further dose reductions were made, which were required for 10 (62%) patients, all of whom had a reduction in their oxaliplatin dose. No chemotherapy drugs were omitted entirely from the planned mFOLFIRINOX treatment regimen.

Two patients who were treated with full-dose FOLFIRINOX in the specified time period were not included in our study cohort. One discontinued therapy after the first cycle due to grade 4 thrombocytopenia and grade 3 nausea; the other patient tolerated two cycles before dose reduction to a modified regimen which was discontinued after a single cycle due to disease progression.

Adverse Events

Treatment-related grade 3 and 4 adverse effects and other toxicity-related events are summarised in table 3 and compared with the toxicity reported with full-dose FOLFIRINOX by Conroy et al. [3]. The incidence of neutropenia was significantly lower with mFOLFIRINOX compared to the full dose (0 vs. 45.7%, $p < 0.001$), with only 1 episode of febrile neutropenia. There was a trend towards less severe fatigue which did not meet statistical significance (5.6 vs. 23.6%, $p = 0.129$). There were no significant differences between the rates of other AEs. Eleven patients (61%) experienced one or more grade 3/4 toxicity and three (16.7%) discontinued treatment as a result. Hospital admission was required in seven cases (38.9%) after a median of two cycles (range 1–12), with details presented in table 4. The most common reasons for hospitalisation were uncontrolled gastrointestinal tract toxicities (five cases) and non-neutropaenic fever (four cases). One patient developed severe dysarthria during oxaliplatin infusion which was attributed to oxaliplatin. This resolved spontaneously within hours and did not recur after dose reduction of oxaliplatin.

Table 1. Patient characteristics

Gender	
Male	8 (44.4)
Female	10 (55.6)
Age, years	
Median	60
Range	40–77
ECOG performance status	
0	10 (56.6)
1	8 (44.4)
Disease localisation	
Head	10 (56.6)
Body	1 (5.6)
Tail	3 (16.7)
Resected	4 (22.2)
Disease site	
Metastatic	15 (83.3)
Locally advanced	3 (16.7)
Biliary stent in situ	
Yes	3 (16.7)
No	15 (83.3)
Values are shown as n (%) unless otherwise indicated.	

Table 2. Treatments delivered and dose reductions

Cycles	8.5 (1–12)
Cycles before dose reduction	2 (1–11)
RDI, %	
5-FU infusion	83.0 (65.9–100)
Oxaliplatin	80.5 (53.3–100)
Irinotecan	64.3 (43.0–75.0)
Dose reduction (total patients)	10 (62.5)
5-FU	4 (25)
Oxaliplatin	10 (62.5)
Irinotecan	3 (18.8)
Values are shown as n (%) or median (range).	

Outcomes

With a median follow-up of 8.9 months (range 3.9–24.0), the median OS and PFS for 15 patients with stage IV disease was 9.3 months (95% CI 8.3–10.4) and 7.2 months (95% CI 4.7–9.6), respectively (fig. 1), all of whom received at least three treatment cycles. At least stable disease by radiological criteria was achieved in 12/15 (80.0%) patients, with 7/15 (46.7%) attaining objective partial responses (table 5).

Table 3. Grade 3 and 4 AEs with mFOLFIRINOX compared with prospective AE data reported with FOLFIRINOX (full dose) [3]

	mFOLFIRINOX (n = 18)	Full dose [3]	p
<i>Adverse events</i>			
<i>Haematological (total)</i>			
Febrile neutropaenia	1 (5.6)	9/166 (5.4)	NS
Neutropaenia	0	75/164 (45.7)	<0.001
Thrombocytopaenia	0	15/165 (9.1)	NS
Anaemia	0	13/166 (7.8)	NS
<i>Non-haematological</i>			
Vomiting	5 (27.8)	24/166 (14.5)	NS
Diarrhoea	3 (16.7)	21/165 (12.7)	NS
Nausea	4 (22.2)	NR	
Fever (non-neutropaenic)	3 (16.7)	NR	
Fatigue	1 (5.6)	39/165 (23.6)	0.13
Dysarthria	1 (5.6)	NR	
Sensory neuropathy	0	15/166 (9.0)	NS
Elevated alanine transaminase	0	12/165 (7.3)	NS
Thromboembolism	0	11/166 (6.6)	NS
<i>Toxicity-related events</i>			
Acute advice/attendance	6 (33.3)	NR	
Hospitalisation	7 (38.9)	NR	
Treatment discontinuation	3 (16.7)	NR	

Values are shown as n (%). NR = Not reported; NS = not statistically significant, p > 0.05.

Table 4. Hospital admissions for AEs

Cycle ^a	Admission duration, days	AEs ^b
1	2	Nausea, vomiting, dysarthria
1	14	Febrile neutropaenia, diarrhoea
1	8	NNF, nausea, fatigue
2	6	NNF, nausea, vomiting
4	2	Vomiting
5	9	NNF
12	–	NNF (grade 2)

NNF = Non-neutropaenic fever.

^a Cycle after which hospital admission was required. ^b Grade 3 or 4 unless otherwise indicated.

Table 5. Best radiological responses

Complete response	1 (6.7)
Partial response	6 (40.0)
Stable disease	5 (33.3)
Progressive disease	3 (20.0)

Values are shown as n (%).

Discussion

The FOLFIRINOX regimen was recently established as an active treatment for unresectable pancreatic adenocarcinoma; however, toxicity has been a major limitation to treatment delivery. In the only phase III study reported to date comparing FOLFIRINOX with gemcitabine alone, both median OS (11.1 vs. 6.8 months) and objective response rate (31.6 vs. 9.4%) were significantly improved by combination chemotherapy. The most commonly occurring grade 3/4 toxicities were neutropaenia (45.7%), fatigue (23.6%), vomiting (14.5%) and diarrhoea (12.7%). Limited fully published evidence exists to support the use of mFOLFIRINOX regimens that are intended to attenuate toxicities whilst preserving efficacy [5, 6, 9, 10]. A summary of study characteristics and outcomes is presented in table 6. In the current report, 5-FU bolus omission was combined with irinotecan 25% dose reduction and routine use of haematopoietic growth factor support.

In line with other studies, the outcome measures for patients with metastatic disease were comparable to those reported for patients undergoing full-dose treatment (table 6), with the caveat that efficacy comparisons based on

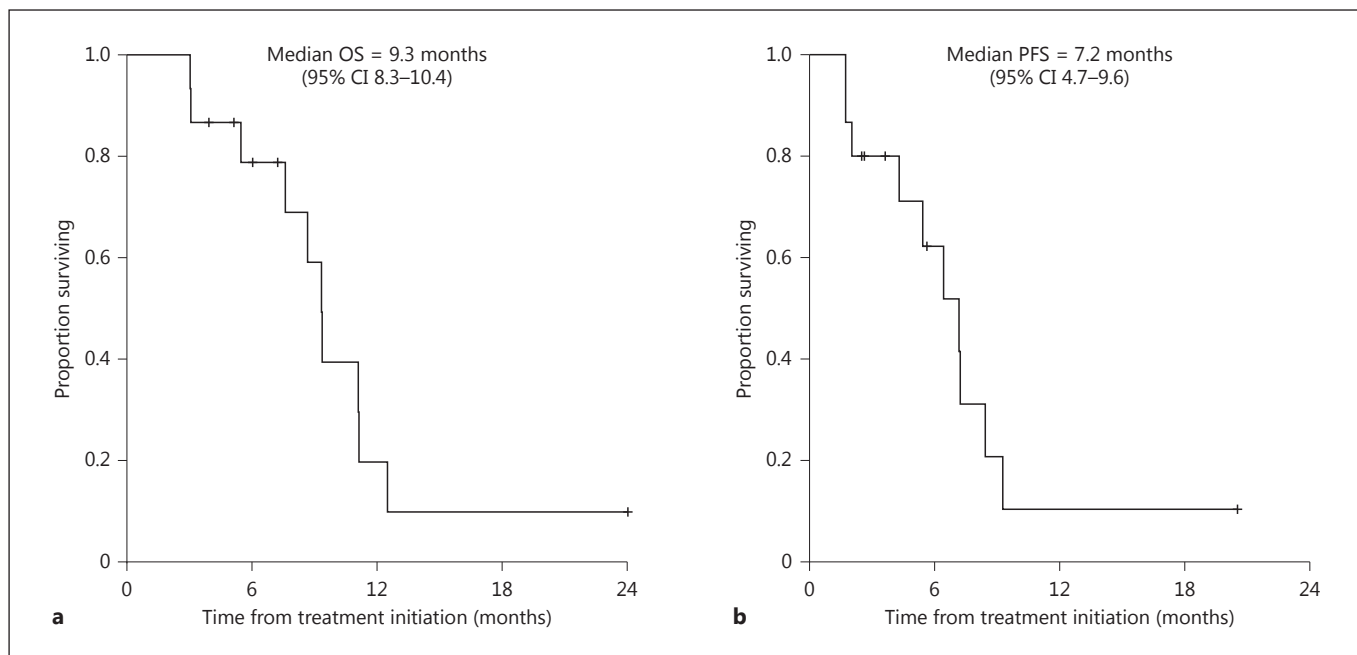


Fig. 1. Kaplan-Meier plots of OS (**a**) and PFS (**b**).

overlap in confidence intervals in median survival statistics is suboptimal, and a randomised phase III study would address this more objectively. Neither the median OS nor the PFS reported here were significantly different from those of the study by Conroy et al. [3] (9.3 vs. 11.1 months and 7.2 vs. 6.4 months, respectively).

In addition, the mFOLFIRINOX regimen we employed had a significantly lower haematological toxicity profile compared to the full-dose treatment, with fewer episodes of grade 3/4 neutropaenia. However, the most frequently occurring non-haematological side effects of diarrhoea and vomiting occurred with comparable frequency to full-dose therapy, with a non-statistically significant reduction in the rate of fatigue.

Although two previous retrospective reports of FOLFIRINOX, where the majority of patients received dose-reduced therapy, have suggested much lower rates of fatigue, nausea and vomiting (<6% in each category) [5, 6], the only published study to specifically evaluate mFOLFIRINOX in the palliative setting reported rates not significantly different to the full dose and closer to those observed here [9]. Similarly, a recently presented prospective phase II study of dose-attenuated treatment found only vomiting and fatigue to be significantly reduced in frequency (2.7 vs. 14.5% and 12.2 vs. 23.3%, respectively), with the incidence of other non-haematological side effects including diarrhoea comparable to full-

dose treatment, and final survival data are awaited [8]. An improved toxicity profile has been reported in the neoadjuvant setting [10]; however, rates of diarrhoea were similar to full-dose therapy. Given the likely superior overall fitness of the operable cohort, these data may not be comparable to results of studies within which a majority of patients had metastatic disease.

In all but one study on the toxicity profile of mFOLFIRINOX, the data are retrospective in nature and therefore can be criticised, as precise identification and grading of AEs cannot be assured. Despite this limitation, harder toxicity endpoints may give a less biased picture. In a total of 121 delivered cycles, three patients (17%) discontinued therapy due to adverse effects, and seven (39%) required hospital admission. This hospitalisation rate is similar to that reported by Peddi et al. [5] of 34% ($n = 21/61$), although the overall toxicity rate was very low in that study (e.g. 3% incidence of diarrhoea). Similarly, Blazer et al. [10] reported a hospital admission rate of 30% ($n = 13/43$). Randomised prospective studies are required to address these discrepancies, and at present, two phase III trials evaluating mFOLFIRINOX in locally advanced disease (NCT01926197) and the adjuvant setting (NCT01526135) are recruiting.

In summary, the mFOLFIRINOX regimen evaluated here was better tolerated than the full-dose treatment with regard to haematological toxicities and also con-

Table 6. Comparison of studies investigating full-dose FOLFIRINOX and mFOLFIRINOX

Study characteristics	Full dose			mFOLFIRINOX		
	Conroy [3]	Peddi [5]	Gunturu [6]	Mahaseeth [9]	Blazer [10]	CUH
Patients, n	166	61	35	60	43	18
Median age, years	61	58	61	63	62.4	60
Stage, %						
Locally advanced	0	37.7	45.7	40	100	16.7
Metastatic	100	62.3	54.3	60	0	83.3
ECOG performance status, %						
0	37.4	NR	69	22	100	56
1	61.9	NR	31	76	100	44
Treatment, mg/m ²						
5-FU bolus	400	400	400	omit	omit	omit
5-FU continuous	2,400/46 h	2,400/46 h	2,400/46 h	2,400/46 h	2,400/46 h	2,400/46 h
Oxaliplatin	85	85	85	85	85	85
Irinotecan	180	180	180	180	165	130
Routine GCSF	no	no	yes	yes	yes	yes
Dose intensity, %						
5-FU bolus	82	57	66	NR	NR	–
5-FU continuous	82	96	100	NR	NR	83
Oxaliplatin	78	96	90	NR	NR	80.5
Irinotecan	81	88	64	NR	NR	64.3
Outcome						
OS, months (95% CI)	11.1 (9.0–13.1)	13.5	11.2	9.0 (7.1–NR)	12.7 ^a (9.6–NR)	9.3 (8.3–10.4)
PFS, months (95% CI)	6.4 (5.5–7.2)	7.5	9.9	8.5 (3.7–11.0)	8.9 ^a (4.5–10.4)	7.2 (4.7–9.6)
ORR, %	31.6	18.2	47	30	23	46.7
Grade 3/4 toxicity, %						
Neutropaenia	45.7	19.7	11.4	3	0	0
Fatigue	23.6	4.9	5.7	13	9.3	5.6
Vomiting	14.5	NR	2.9	8	0	27.8
Diarrhoea	12.7	3.3	2.9	13	14.0	16.7

CUH = Cambridge University Hospitals NHS Foundation Trust; GCSF = granulocyte colony-stimulating factor; NR = not reported; ORR = objective response rate.

^a Results for non-resected patients.

ferred a marginal benefit in non-haematological AE rates, without compromising efficacy. A significant proportion (42.5%) of patients within the initial phase III study of FOLFIRINOX required filgrastim; therefore, the question remains to be answered whether routine addition of filgrastim to full-dose FOLFIRINOX as primary prophylaxis would result in similar tolerability as modified dose regimens. Although some studies have reported significant improvements in side effect profile with dose attenuation, our findings are not in keeping with this. Wide variations in toxicity rates between studies may be accounted for by the limitations of retrospective AE profiling. The high hospitalisation rate observed here and elsewhere serves as a more objective indicator of the toxicity of this combination, and rigorous anti-emetic and anti-

diarrhoeal management is strongly recommended. The potential benefits of mFOLFIRINOX remain to be proven, and the results of ongoing prospective studies are awaited to formally evaluate the safety and outcomes of these regimens.

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Disclosure Statement

The authors have no conflicts of interests to declare.

References

- ▶1 Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JWW, Comber H, et al: Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013;49:1374–1403.
- ▶2 De Angelis R, Sant M, Coleman MP, Francis S, Baili P, Pierannunzio D, et al: Cancer survival in Europe 1999–2007 by country and age: results of EUROCare-5 – a population-based study. *Lancet Oncol* 2014;15:23–34.
- ▶3 Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817–1825.
- ▶4 Conroy T, Gavaille C, Samalin E, Ychou M, Ducreux M: The role of the FOLFIRINOX regimen for advanced pancreatic cancer. *Curr Oncol Rep* 2013;15:182–189.
- ▶5 Peddi PPF, Lubner S, McWilliams R, Tan BR, Picus J, Sorscher SM, et al: Multi-institutional experience with FOLFIRINOX in pancreatic adenocarcinoma. *JOP* 2012;13:497–501.
- ▶6 Gunturu KS, Yao X, Cong X, Thumar JR, Hochster HS, Stein SM, et al: FOLFIRINOX for locally advanced and metastatic pancreatic cancer: single institution retrospective review of efficacy and toxicity. *Med Oncol* 2013;30:361.
- ▶7 Ginocchi L, Vasile E, Caponi S, Lucchesi M, Caparello C, Lencioni M, et al: Modified FOLFOXIRI in advanced pancreatic cancer. *JOP* 2012;13:563.
- 8 James ES, Cong X, Yao X, Hahn C, Kaley K, Li J, et al: Final analysis of a phase II study of Yale-modified FOLFIRINOX (mFOLFIRINOX) in metastatic pancreatic cancer (MPC). 2015 Gastrointestinal Cancers Symposium. *J Clin Oncol* 2015;33:abstr 395.
- ▶9 Mahaseth H, Brucher E, Kauh J, Hawk N, Kim S, Chen Z, et al: Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. *Pancreas* 2013;42:1311–1315.
- ▶10 Blazer M, Wu C, Goldberg RM, Phillips G, Schmidt C, Muscarella P, et al: Neoadjuvant modified (m) FOLFIRINOX for locally advanced unresectable (LAPC) and borderline resectable (BRPC) adenocarcinoma of the pancreas. *Ann Surg Oncol* 2015;22:1153–1159.
- 11 Lee J, Lee YS, Paik K, Kim HW, Kim J, Hwang J: Does reduced dose of FOLFIRINOX guarantee tumor response in unresectable pancreatic cancer? Suggestion for the minimal relative dose intensity. *Ann Oncol* 2014;25(suppl 4):iv210–iv253.
- ▶12 Hryniuk W, Bush H: The importance of dose intensity in chemotherapy of metastatic breast cancer. *J Clin Oncol* 1984;2:1281–1288.

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Appendix GOURGOU01

Impact of FOLFIRINOX Compared With Gemcitabine on Quality of Life in Patients With Metastatic Pancreatic Cancer: Results From the PRODIGE 4/ACCORD 11 Randomized Trial

Sophie Gourgou-Bourgade, Caroline Bascoul-Mollevi, Françoise Desseigne, Marc Ychou, Olivier Bouché, Rosine Guimbaud, Yves Bécouarn, Antoine Adenis, Jean-Luc Raoul, Valérie Boige, Jocelyne Bérille, and Thierry Conroy

See accompanying editorial on page 3

ABSTRACT

Purpose

To compare the quality of life (QoL) of patients receiving oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) or gemcitabine as first-line chemotherapy and to assess whether pretreatment QoL predicts survival in patients with metastatic pancreatic cancer.

Patients and Methods

Three hundred forty-two patients with performance status 0 or 1 were randomly assigned to receive FOLFIRINOX (oxaliplatin, 85 mg/m²; irinotecan, 180 mg/m²; leucovorin, 400 mg/m²; and fluorouracil, 400 mg/m² bolus followed by 2,400 mg/m² 46-hour continuous infusion, once every 2 weeks) or gemcitabine 1,000 mg/m² weekly for 7 of 8 weeks and then weekly for 3 of 4 weeks. QoL was assessed using European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire C30 every 2 weeks.

Results

Improvement in global health status (GHS; $P < .001$) was observed in the FOLFIRINOX arm and improvement in emotional functioning ($P < .001$) was observed in both arms, along with a decrease in pain, insomnia, anorexia, and constipation in both arms. A significant increase in diarrhea was observed in the FOLFIRINOX arm during the first 2 months of chemotherapy. Time until definitive deterioration ≥ 20 points was significantly longer for FOLFIRINOX compared with gemcitabine for GHS, physical, role, cognitive, and social functioning, and six symptom domains (fatigue, nausea/vomiting, pain, dyspnea, anorexia, and constipation). Physical functioning, constipation, and dyspnea were independent significant prognostic factors for survival with treatment arm, age older than 65 years, and low serum albumin.

Conclusion

FOLFIRINOX significantly reduces QoL impairment compared with gemcitabine in patients with metastatic pancreatic cancer. Furthermore, baseline QoL scores improved estimation of survival probability when added to baseline clinical and demographic variables.

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INTRODUCTION

We have previously reported the efficacy and safety of the oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) regimen versus gemcitabine as first-line therapy among patients with metastatic pancreatic adenocarcinoma (mPAC).¹ The results showed significantly longer overall survival (OS) but increased toxicity with FOLFIRINOX. Health-related quality of life (QoL) is paramount to patients with mPAC because most have high levels of symptoms when diagnosed

and because life expectancy is usually short. Using a validated instrument, the European Organization for the Research and Treatment of Cancer QoL Questionnaire C30 (EORTC QLQ-C30) version 3.0,² we prospectively assessed longitudinal QoL as a secondary end point of the PRODIGE (Partenariat de Recherche en Oncologie Digestive) /ACCORD (Actions Concertées dans les Cancers Colo-Rectaux et Digestifs) phase III trial.

We have, in part, previously reported the results of the QoL analysis based on EORTC QLQ-C30 scales that are usually most affected in

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patients with pancreatic cancer (global health status [GHS], fatigue, pain, physical functioning (PF), emotional functioning, and role functioning); other domains were examined in an exploratory manner.¹ Time until definitive deterioration (TUDD) of the QoL domains was analyzed for a 10-point minimal clinically important difference (MCID).

The aim of our article is to provide detailed analysis of QoL data for all domains. We extended the analysis to include TUDD using a more stringent and clinically relevant 20-point MCID cutoff.³ Furthermore, we performed a multivariate analysis to determine the prognostic value of baseline QoL measures for survival.

PATIENTS AND METHODS

Trial Design

Adult patients with measurable mPAC, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 or 1, and no prior chemotherapy were eligible for inclusion in this open-label, multicenter, randomized, phase II/III trial. Detailed inclusion and exclusion criteria, study design, and protocol have been published previously.¹

Gemcitabine 1,000 mg/m² was infused weekly for 7 weeks, followed by a 1-week rest period, and then once per week for 3 weeks of a 4-week cycle. FOLFIRINOX consisted of oxaliplatin 85 mg/m² as a 2-hour intravenous infusion immediately followed by leucovorin 400 mg/m² administered as a 2-hour intravenous infusion and, after 30 minutes, with irinotecan 180 mg/m² as a 90-minute intravenous infusion; this was followed by a fluorouracil 400 mg/m² intravenous bolus and then continuous intravenous infusion of 2,400 mg/m² over 46 hours once every 2 weeks. Six months of chemotherapy was recommended for patients who had a response. Details of treatment have been published previously.¹

The cutoff date for the current QoL analysis was April 16, 2010, the date used for the original efficacy and safety assessment.¹

QoL Measurement

QoL was measured using EORTC QLQ-C30, version 3.0,² which is a validated, cancer-specific instrument designed for prospective clinical trials. The EORTC QLQ-C30 questionnaire evaluates five functions (physical, role, cognitive, emotional, and social), nine symptoms (fatigue, pain, nausea and vomiting, dyspnea, loss of appetite, insomnia, constipation, diarrhea, and financial difficulties) and the GHS/QoL. This questionnaire adequately covers the main problems and symptoms presented by patients with mPAC. Its psychometric properties and high acceptability rate in the French language have been confirmed.⁴

Questionnaires were to be completed at baseline before random assignment and every 2 weeks until progression. Questionnaires were completed in the clinic before interaction with health care personnel. Because of the multitude of QoL evaluations, we simplified the number of observations to calculate compliance to include baseline, day 15, day 30, and months 2, 4, 6, 8, and 10.

The description of QoL scores are therefore reported for these respective time points, whereas all QoL questionnaires were used for longitudinal analyses. Responses to the questionnaire were transformed into 0 to 100 scores, with a high score implying a high level of symptoms or a high level of functioning or global QoL.

Statistical Analysis

Analysis of findings from the EORTC QLQ-C30 questionnaires followed EORTC guidelines.⁵ All analyses were performed in the intent-to-treat population. Comparison of the scores between treatment arms was performed with the Kruskal-Wallis test. Comparison between the baseline and the end of treatment was performed using the Sign rank test. Internal consistency of the questionnaire was estimated by using Cronbach's alpha for each dimension and visit. Values greater than .7 are generally regarded as acceptable, greater than .8 as good, and greater than .9 as excellent.⁶ An additional longitudinal analysis was performed based on a survival analysis method.⁷ This involves survival methods in which the definitive deterioration of QoL score is considered as an event.

Table 1. Baseline Demographic and Clinical Characteristics of Patients in the Intent-to-Treat Population

Characteristic	FOLFIRINOX (n = 171)		Gemcitabine (n = 171)	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	61		61	
Range	25-76		34-75	
Sex				
Male	106	62	105	61
Female	65	38	66	39
ECOG performance status				
0	64	37	66	39
1	106	62	105	61
2	1	< 1	0	0
Pancreatic tumor location				
Head	67	39	63	37
Body	53	31	58	34
Tail	45	26	45	26
Multicentric	6	4	5	3
Metastatic sites involved				
Median	2		2	
Range	1-6		1-6	
Measurable metastatic sites*				
Liver	149	88	150	88
Pancreas	90	53	91	53
Lymph node	49	29	39	23
Lung	33	19	49	29
Peritoneal	33	19	32	19
Other	18	11	29	17

NOTE. Reproduced with permission from Conroy et al.¹

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FOLFIRINOX, oxaliplatin/irinotecan/fluorouracil/leucovorin.

*Denominator 170 for the FOLFIRINOX arm.

Osoba et al³ showed that a mean change of 5 to 10 points in a QLQ-C30 score corresponds to a "little" change in QoL, a change of 10 to 20 points corresponds to a "moderate" change, and a change of more than 20 points corresponds to a "large" change. We used this definition when appropriate to indicate the clinical relevance of any differences observed. For a given baseline score, QLQ-C30 score was considered definitive deterioration if this score decreased by more than 10 points (or 20 points) as compared with the score at baseline, without later improvement superior to 10 points (or 20 points) as compared with baseline or without any available score. Thus, TUDD for QoL scores was defined as the time from randomization to the first observation of a definitive deterioration of QLQ-C30 score. Similarly, TUDD was reanalyzed by integrating death as an event. TUDD was analyzed with the use of the Kaplan-Meier method; the log-rank test was used to compare treatment arms.

Multivariate analysis was performed to determine baseline prognostic factors for OS, following the method previously published in an EORTC meta-analysis.⁸ OS was calculated from the date of random assignment to the date of death, with living patients censored at the last date of follow-up before the cutoff for analysis. We investigated the prognostic value of QoL scores in complementing the prognostic model based on clinical data. Synchronous metastases, a low baseline albumin (< 3.5 g/dL), liver metastases, age older than 65 years, and treatment arm were previously identified as independent prognostic factors for OS.¹ Initially, each baseline QLQ-C30 dimension was tested in a univariate model to identify prognostic variables for OS ($P < .05$) and was added to a Cox model stratified by ECOG score (0 v 1) and primary tumor localization (head v other sites) containing clinical data. A proportional hazards assumption was verified using Schoenfeld residuals. The predictive power of the models identified was assessed according to Harrell's discrimination C-index.⁹ The Harrell's C-index is a probability of concordance between

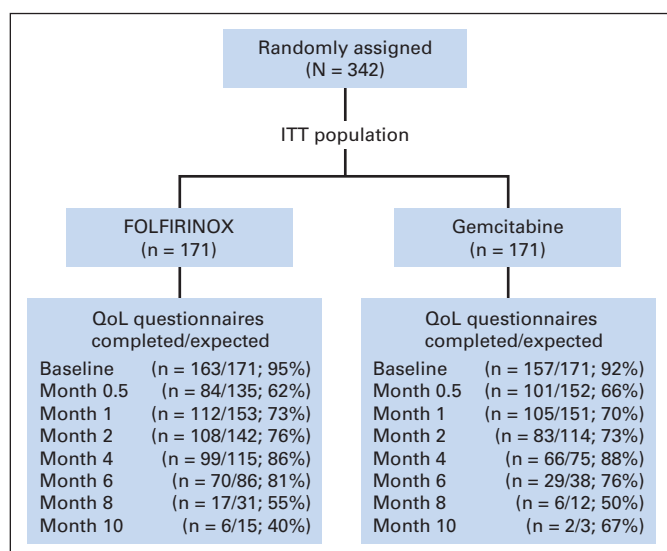


Fig 1. CONSORT diagram for European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaires C30 completed for the total number of eligible patients at different time points in each treatment group. FOLFIRINOX, oxaliplatin/irinotecan/fluorouracil/leucovorin; ITT, intent to treat; QoL, quality of life.

predicted and observed survival, a value of 1 indicates perfect concordance of the score and outcome, whereas a value of .5 indicates only chance agreement.¹⁰ All analyses were performed with STATA software, version 11.0 (STATA, College Station, TX).

RESULTS

Patient Characteristics

A total of 342 patients were enrolled between December 2005 and October 2009; the intent-to-treat population comprised 171 patients

in each arm. The median follow-up was 26.6 months (95% CI, 20.5 to 44.9). Baseline demographic and disease characteristics were similar for both treatment arms (Table 1), except there were fewer measurable lung metastases in the FOLFIRINOX arm compared with the gemcitabine arm.

Baseline compliance with completion of QLQ-C30 questionnaires was high: 163 questionnaires (95%) and 157 questionnaires (92%) in the FOLFIRINOX and gemcitabine arms, respectively, and there was no difference between the patients who completed baseline QoL forms and those who did not (Figure 1). Despite the fact that ECOG PS was 0 or 1 at inclusion according to the physician, 30 patients (18.4%) in the FOLFIRINOX arm and 26 patients (16.6%) in the gemcitabine arm answered “quite a bit” (11.6%) or “very much” (6%) at the baseline item “Do you need to stay in bed or a chair during the day?”. These patients had a worse prognosis than the overall population with a median OS of 6.7 months and 4.6 months in the FOLFIRINOX and the gemcitabine arms, respectively. In the FOLFIRINOX group, the survival difference between patients who answered they have no need to rest and those who needed to rest is significant, with median survival of 12.6 months and 6.7 months, respectively ($P = .03$). In the gemcitabine arm, the median survival in these groups is not significantly different, 6.7 versus 4.6 months.

Compliance for questionnaire completion over time in surviving patients varied between 40% to 95%. The rate of assessable questionnaires decreased after the 6-month treatment period, as expected. The rates of missing questionnaires were comparable between both treatments during follow-up.

There was no statistically significant difference between treatment arms with respect to baseline QLQ-C30 QoL domains or single items (Appendix Table A1 [online-only]). Functional scores were high and the most marked symptoms were anorexia, fatigue, pain, insomnia, and constipation.

Table 2. Univariate Cox Analysis According to 10-Point and 20-Point MCID to Calculation of TUDD for QLQ-C30 Domain Scores

Domain	10-Point Deterioration					20-Point Deterioration				
	No. of Events		HR	95% CI	P	No. of Events		HR	95% CI	P
	FOLFIRINOX (n = 163)	Gemcitabine (n = 157)				FOLFIRINOX (n = 163)	Gemcitabine (n = 157)			
Global health status	32	42	2.3	1.4 to 3.7	< .001	13	32	4.7	2.3 to 9.5	< .001
Physical functioning	47	59	1.9	1.3 to 2.8	.001	27	37	2.2	1.3 to 3.6	.001
Role functioning	44	59	2.2	1.5 to 3.4	< .001	27	43	2.7	1.6 to 4.4	< .001
Emotional functioning	18	26	2.9	1.6 to 5.6	< .001	14	14	2.1	1.0 to 4.5	.057
Cognitive functioning	30	49	3.0	1.9 to 4.8	< .001	11	16	2.6	1.2 to 5.6	.015
Social functioning	42	54	2.1	1.4 to 3.1	< .001	23	40	2.7	1.6 to 4.7	< .001
Fatigue	52	62	1.9	1.3 to 2.7	.001	36	49	2.4	1.5 to 3.8	< .001
Nausea/vomiting	40	53	2.1	1.4 to 3.2	< .001	19	30	2.8	1.5 to 5.0	< .001
Pain	27	36	2.7	1.6 to 4.6	< .001	12	22	3.7	1.7 to 7.7	< .001
Dyspnea	32	38	2.3	1.4 to 3.8	< .001	32	38	2.3	1.4 to 3.8	< .001
Insomnia	20	15	1.4	0.7 to 2.9	.300	20	15	1.4	0.7 to 2.9	.300
Loss of appetite	24	28	1.9	1.1 to 3.4	.022	24	28	1.9	1.1 to 3.4	.022
Constipation	18	21	2.0	1.0 to 3.8	.033	18	21	2.0	1.0 to 3.8	.033
Diarrhea	37	32	1.5	0.9 to 2.5	.086	37	32	1.5	0.9 to 2.5	.086
Financial difficulties	22	8	0.6	0.2 to 1.4	.214	22	8	0.6	0.2 to 1.4	.214

NOTE. For global health status and functional scales, a high score indicates a better function. For symptoms and financial difficulties, a high score indicates more symptoms or more difficulties.

Abbreviations: FOLFIRINOX, oxaliplatin/irinotecan/fluorouracil/leucovorin; HR, hazard ratio; MCID, minimal clinically important difference; QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; TUDD, time until definitive deterioration.

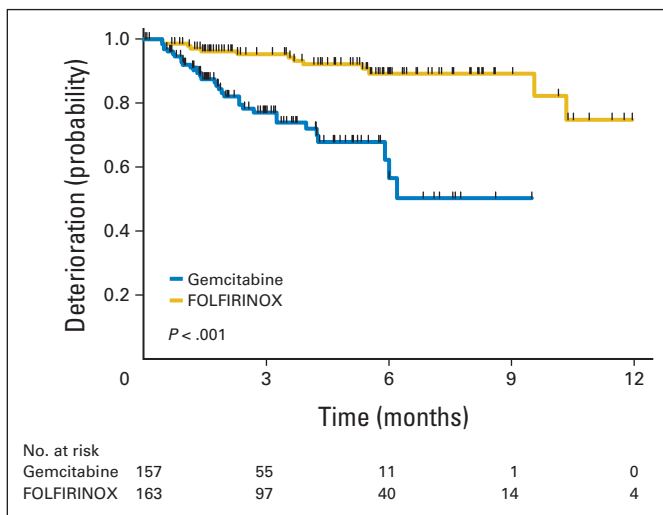


Fig 2. Kaplan-Meier plot for time until definitive deterioration more than 20 points for European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire C30 global health status/quality of life. FOLFIRINOX, oxaliplatin/irinotecan/fluorouracil/leucovorin.

Longitudinal Analysis

Cronbach's alpha of all domains was calculated and was more than .85, confirming the internal consistency of the questionnaire in this population. When comparing the treatment arms, there did not appear to be any difference in the change in QLQ-C30 domains over time, except for diarrhea. The change in GHS over time was similar when comparing the treatment arms (Appendix Fig A1A [online-only]). GHS scores improved ($P < .001$) in the FOLFIRINOX arm and emotional functioning scores improved ($P < .001$) in both arms between baseline and the end of treatment (6 months). Similarly, a decrease in four symptom scores (pain: FOLFIRINOX, $P < .001$; gemcitabine, $P = .01$; insomnia: FOLFIRINOX, $P < .001$; gemcitabine, $P = .005$; anorexia: FOLFIRINOX, $P < .001$; gemcitabine, $P = .02$; and constipation: FOLFIRINOX, $P = .002$; gemcitabine, $P = .02$) was found for both treatments. Patients experienced more diarrhea on the FOLFIRINOX arm than on the gemcitabine arm during the first 2 months of treatment (Appendix Fig A1N; $P = .009$). The other functional and symptom domains are presented in Appendix Figure A1. The percentage of patients with a worsening or improvement of ≥ 10 points each scores are also listed in Appendix Table A2. A moderate improvement of GHS score (≥ 10 points) was found in 30.1% and 18.5% of the patients, in the FOLFIRINOX and gemcitabine arms, respectively. Improvement in fatigue and dyspnea scores was significantly associated with treatment response in both arms, as were the scores for GHS, pain, and insomnia in the FOLFIRINOX arm.

Time Until Definitive Deterioration Analysis

TUDD was determined according to a MCID of at least 10 or 20 points in QLQ-C30 scores for the different domains in both arms (Table 2). TUDD ≥ 10 points was significantly longer for the FOLFIRINOX versus the gemcitabine arm for GHS/QoL, all five functional domains, and six symptom domains (fatigue, nausea/vomiting, pain, dyspnea, anorexia, and constipation). In general, significance was maintained for TUDD ≥ 20 points, except for the emotional functioning domain. The TUDD ≥ 10 points (hazard ratio [HR], 2.3; 95% CI, 1.4 to 3.7; $P < .001$) and ≥ 20 points (HR, 4.7; 95% CI, 2.3 to 9.5; $P < .001$) for GHS score were longer in the FOLFIRINOX arm. Median TUDD of GHS/QoL score was not reached in the FOLFIRINOX arm unlike the gemcitabine arm (Fig 2). Similar results were observed with the TUDD including death as an event (results not shown).

Prognostic Factors for Survival

Univariate Cox analysis revealed the following QLQ-C30 domains as significant prognostic factors for OS for the intent-to-treat population including both treatment arms: PF (HR, 0.88; 95% CI, 0.82 to 0.94; $P < .001$); role functioning (HR, 0.94; 95% CI, 0.90 to

Table 3. Multivariate Analysis of Overall Survival

Variable	Model 0*			Model 1†			Model 2‡			Model 3§		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Baseline clinical and demographic characteristics												
Treatment arm	0.54	0.41 to 0.72	< .001	0.49	0.36 to 0.66	< .001	0.45	0.33 to 0.62	< .001	0.50	0.37 to 0.68	< .001
Age > 65 years	1.45	1.06 to 1.99	.023	1.51	1.09 to 2.09	.012	1.63	1.16 to 2.27	.018	1.55	1.12 to 2.15	.009
Low serum albumin	1.85	1.38 to 2.49	< .001	1.71	1.25 to 2.34	< .001	1.62	1.17 to 2.23	< .001	1.68	1.23 to 2.29	< .001
Synchronous metastases	0.41	0.21 to 0.77	.002							0.69	0.35 to 1.37	.277
Liver metastases	1.62	1.03 to 2.55	.028	1.69	1.05 to 2.71	.022	1.94	1.19 to 3.16	.010	1.60	0.99 to 2.59	.045
Baseline QLQ-C30 domain score												
Physical functioning				0.91	0.84 to 0.99	.039	0.88	0.81 to 0.96	.010	0.91	0.84 to 0.99	.040
Constipation				1.06	1.01 to 1.11	< .001	1.06	1.01 to 1.12	< .001	1.06	1.01 to 1.11	< .001
Dyspnea				1.07	1.00 to 1.14	.001	1.10	1.02 to 1.18	< .001	1.06	1.00 to 1.14	.001
Pain							0.93	0.87 to 0.99	.063			

Abbreviations: HR, hazard ratio; QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30.

*Model 0: Base model includes only clinical and demographic characteristics.

†Model 1: Final model for backward selection using the five significant clinical and demographic variables (Model 0) plus the six QLQ-C30 domains that were significant on univariate analysis (physical functioning, role functioning, fatigue, constipation, dyspnea, and loss of appetite).

‡Model 2: Final model for forward selection using the variables selected by backward selection (Model 1) plus the nine QLQ-C30 domains that were not significant on univariate analysis (global health status, emotional functioning, cognitive functioning, social functioning, nausea/vomiting, pain, insomnia, diarrhea, and financial difficulties).

§Model 3: Final model excluding pain because of interaction and forcing the variable of the time of appearance of hepatic metastases.

0.98; $P = .005$); fatigue (HR, 1.07; 95% CI, 1.02 to 1.13; $P = .007$); constipation (HR, 1.06; 95% CI, 1.02 to 1.11; $P = .001$); dyspnea (HR, 1.08; 95% CI, 1.03 to 1.13; $P = .004$); and anorexia (HR, 1.06; 95% CI, 1.02 to 1.11; $P = .001$). These six univariate QLQ-C30 domains were added to the base model (model 0) that included the significant clinical and demographic prognostic variables for OS (treatment arm, age > 65 years, low serum albumin, synchronous metastases, and liver metastases) for backward selection (model 1) and forward selection (model 2; Table 3). Only PF, constipation, and dyspnea remained significant after the backward and forward selection procedures. The presence of liver metastases no longer remained significant after the addition of QLQ-C30 domains in the model. However, the presence of liver metastases was forced as a prognostic factor in the final model (model 3) to better measure the contribution of QoL to the clinical model as prognostic factors.

To complete the analysis of prognostic factors for QLQ-C30 data, we determined the Harrell predictive C-index. Two models were compared: a model with the five significant clinical and demographic prognostic variables and another model with the same variables plus the significant QLQ-C30 domains (PF, constipation, and dyspnea). The predictive value added to the three QLQ-C30 domains to the clinical model improved the predictive power by 7.5%, as the predictive power changed from 0.66 to 0.71. Survival curves in different subgroups for baseline QLQ-C30 scores by tercile for PF, constipation, and dyspnea are shown in Figure 3. Severely compromised baseline PF in the lower tercile (ie, less than 33.3 points) seemed to have the most dramatic negative impact on OS, with a median OS of 2.1 months versus 9 months for patients with PF score of more than 66.6 (Fig 3A). The GHS score at baseline and the early improvement of GHS score (within the first 1 or 2 months) are not predictive of a better OS (data not shown).

DISCUSSION

In our original trial, we demonstrated that the FOLFIRINOX regimen is an effective first-line treatment option for patients with mPAC with good PS.¹ Median OS (11.1 v 6.8 months; HR, 0.57; 95% CI, 0.45 to 0.73; $P < .001$) and progression-free survival (6.4 v 3.3 months; HR, 0.47; 95% CI, 0.37 to 0.59; $P < .001$) were significantly prolonged in patients receiving FOLFIRINOX compared with those receiving gemcitabine, which was considered to be a clinically meaningful improvement.¹¹⁻¹⁵ However, the safety of FOLFIRINOX was less favorable than gemcitabine, producing higher incidences of neutropenia, febrile neutropenia, thrombocytopenia, diarrhea, and sensory neuropathy. It is therefore important to analyze the impact of treatment on QoL in relation to patient outcome.

A potential source of bias is the proportion of missing QoL forms over the assessment period. However, there was no difference in the rate of missing data between the two arms with a good compliance rate until 6 months. After 6 months, the population was reduced as a result of progressive disease and end of treatment period.

As expected, there were no notable differences between treatment arms over time for EORTC QLQ-30 domains with the exception of diarrhea, which seemed to be negatively affected in the FOLFIRINOX arm during the first 2 months of treatment. However, TUDD ≥ 10 points was significantly longer in the FOLFIRINOX arm for all QLQ-C30 domains (except insomnia, diarrhea, and financial difficulties). Significance was maintained for a TUDD ≥ 20 points for the

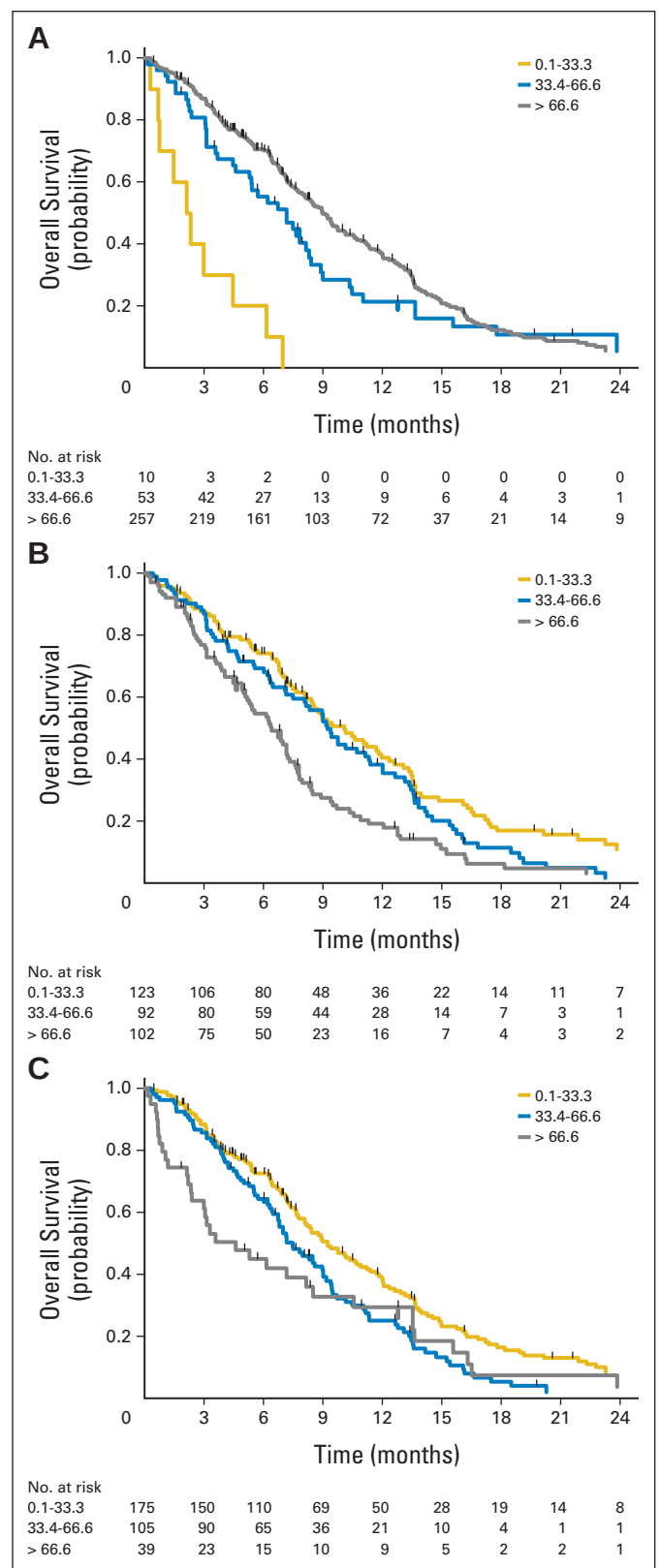


Fig 3. Kaplan-Meier overall survival plots according to baseline tercile point score of significant prognostic European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire C30 domains (A) physical functioning, (B) constipation, and (C) dyspnea.

aforementioned QLQ-C30 domains except emotional functioning. The longer TUDD ≥ 10 points (HR, 2.3; 95% CI, 1.4 to 3.7; $P < .001$) and ≥ 20 points (HR, 4.7; 95% CI, 2.3 to 9.5; $P < .001$) for GHS score in the FOLFIRINOX arm versus the gemcitabine arm showed a more powerful result when using the more stringent MCID cutoff. The results for a TUDD ≥ 20 points confirm a clinically meaningful prolongation of QoL in patients treated with FOLFIRINOX as compared with gemcitabine despite its less favorable safety.

Another aim of this study was to determine the prognostic value of baseline QLQ-C30 domain scores with respect to survival. This analysis revealed three significant QLQ-C30 domains (PF, constipation, and dyspnea) when added to a model including significant clinical and demographic prognostic variables (treatment arm, age > 65 years, low serum albumin, synchronous metastases, and hepatic metastases). Severely impaired baseline PF seemed to impart the strongest negative impact on OS. This result is particularly important considering that this population was selected on good PS (ECOG 0 or 1) according to the physician's assessment. However, 56 patients (17.4%) wrote in their baseline QoL questionnaire that they needed to stay in bed or a chair during the day. These patients had a worse prognosis, and this result suggests that the PF score of the EORTC QLQ-C30 is a more comprehensive measure of QoL than PS and has a strong prognostic value. The highest prognostic value of patient self-assessment of QoL compared with physician rating of PS has been reported in other studies.^{8,16-17}

To our knowledge, there have been no other studies that have determined the impact of baseline QLQ-C30 QoL measures on survival outcome specifically in mPAC, although other QoL measures have been analyzed occasionally in smaller and/or less homogeneous populations. In a meta-analysis of randomized trials including 7,417 patients with cancer who filled out baseline QLQ-C30 questionnaires,⁸ multivariate analysis revealed that PF, pain, and anorexia were significant prognostic variables in addition to age, gender, and distant metastases, but not WHO PS. A literature review¹⁸ detailed the relationship between QoL and survival in cancer. Global QoL, functional domains, appetite loss, fatigue, and pain scores were the most prognostic indicators for OS. However, none of the studies identified in this review or our own review of the literature involved homogeneous populations with pancreatic cancer with baseline EORTC QLQ-C30 evaluation. The prognostic values of other QoL scales have been studied in patients with pancreatic cancer. In 55 patients,¹⁹ the health and physical subscale of the Ferrans and Powers QoL Index was shown to be a marginally significant predictor of survival after controlling for the stage at diagnosis. In 86 patients with cachexia,²⁰ baseline fatigue and PF scores predicted OS using various QoL measures, but multivariate analysis was not performed. The prognostic value of various

QoL indicators (including global linear-analog self-assessment indicators) was recently reported in 319 patients with advanced pancreatic cancer; baseline pain and tiredness were independent prognostic factors for OS but less so than baseline carbohydrate antigen 19-9.²¹

In conclusion, our analysis confirms that FOLFIRINOX significantly reduces QoL impairment compared with gemcitabine in patients with mPAC. Furthermore, multivariate analysis showed the additional prognostic value of baseline EORTC QLQ-C30 measures when added to clinical and demographic variables to predict survival among patients with mPAC. Whether or not baseline PF QoL score should be used as a stratification factor in further clinical trials has to be assessed prospectively.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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REFERENCES

- Conroy T, Desseigne F, Ychou M, et al: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 364:1817-1825, 2011
- Aaronson NK, Ahmedzai S, Bergman B, et al: The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 85:365-376, 1993
- Osoba D, Rodrigues G, Myles J, et al: Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 16:139-144, 1998

- Conroy T, Mercier M, Bonnetterre J, et al: French version of FACT-G: Validation and comparison with other cancer-specific instruments. *Eur J Cancer* 40:2243-2252, 2004
- Fayers P, Aaronson N, Boral K, et al: EORTC QLQ-C30 Scoring Manual. Brussels, Belgium, European Organisation for Research and Treatment of Cancer, 2001
- Cronbach LJ: Coefficient alpha and the internal structure of tests. *Psychometrika* 16:297-334, 1951
- Bonnetain F, Dahan L, Maillard E, et al: Time until definitive quality of life score deterioration as a means of longitudinal analysis for treatment trials in patients with metastatic pancreatic cancer. *Eur J Cancer* 46:2753-2762, 2010

- Quinten C, Coens C, Mauer M, et al: Baseline quality of life as a prognostic indicator of survival: A meta-analysis of individual patient data from EORTC clinical trials. *Lancet Oncol* 10:865-871, 2009
- Harrell FE Jr, Lee KL, Mark DB: Multivariable prognostic models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 15:361-387, 1996
- Harrell F: Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression and Survival Analysis. New York, NY, Springer, 2001
- Kris MG, Benowitz SI, Adams S, et al: Clinical cancer advances 2010: Annual report on progress

against cancer from the American Society of Clinical Oncology. *J Clin Oncol* 28:5327-5347, 2010

12. Kim R: FOLFIRINOX: A new standard treatment for advanced pancreatic cancer? *Lancet Oncol* 12:8-9, 2011

13. Ko AH: FOLFIRINOX: A small step or a great leap forward? *J Clin Oncol* 29:3727-3729, 2011

14. Saif MW, Chabot J: Chemotherapy: Metastatic pancreatic cancer—Is FOLFIRINOX the new standard? *Nat Rev Clin Oncol* 8:452-453, 2011

15. Vaccaro V, Sperduti I, Milella M: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 365:768-769, 2011 (author reply 769)

16. Efficace F, Bottomley A, Coens C, et al: Does a patient's self-reported health-related quality of life predict survival beyond key biomedical data in advanced colorectal cancer? *Eur J Cancer* 42:42-49, 2006

17. Gotay CC, Kawamoto CT, Bottomley A, et al: The prognostic significance of patient-reported outcomes in cancer clinical trials. *J Clin Oncol* 26:1355-1363, 2008

18. Montazeri A: Quality of life as prognostic indicators of survival in cancer patients: An overview of the literature from 1982 to 2008. *Health Qual Life Outcomes* 7:102, 2009

19. Lis CG, Gupta D, Grutsch JF: Patient satisfaction with quality of life as a predictor of survival in

pancreatic cancer. *Int J Gastrointest Cancer* 37:35-44, 2006

20. Robinson DW Jr, Eisenberg DF, Cella D, et al: The prognostic significance of patient-reported outcomes in pancreatic cancer cachexia. *J Support Oncol* 6:283-290, 2008

21. Bernhard J, Dietrich D, Glimelius B, et al: Estimating prognosis and palliation based on tumor marker CA 19-9 and quality of life indicators in patients with advanced pancreatic cancer receiving chemotherapy. *Br J Cancer* 103:1318-1324, 2010



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Appendix GUNTURU02

FOLFIRINOX for locally advanced and metastatic pancreatic cancer: single institution retrospective review of efficacy and toxicity

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Abstract Although FOLFIRINOX significantly increases survival in metastatic pancreatic cancer (MPC) compared to gemcitabine (Conroy et al. *N Engl J Med* 364:1817–1825, 2011), toxicities have tempered enthusiasm for its use in full doses. To assess the impact of dose attenuations on toxicity and efficacy, we reviewed our institution's experience with FOLFIRINOX in locally advanced pancreatic cancer (LAPC) and MPC. We performed a retrospective review of dose, toxicity, and efficacy of FOLFIRINOX in all patients with LAPC and MPC treated between June 2010 and July 2011 at Yale. Toxicities in all patients and response rate (RR) and survival in previously untreated MPC were compared to data reported by Conroy. Overall survival (OS) and progression-free survival were estimated by Kaplan–Meier method. Thirty-five patients were treated (16 LAPC; 19 MPC). Twenty-nine patients received dose attenuations with the first cycle. Median relative doses of irinotecan and bolus fluorouracil were less than those reported by Conroy (64 vs. 81 % and 66 vs. 82 %, respectively). RR was 50 % in LAPC and 47 % in MPC, and the latter did not differ significantly from the RR reported by Conroy ($p = 0.19$). OS at 6 and 12 months in MPC was comparable to OS reported by Conroy. Grade 3/4 toxicities were less than reported by Conroy, including fatigue ($p = 0.009$) and neutropenia ($p < 0.0001$). Nine patients experienced transient dysarthria during irinotecan administration. Our findings validate

the efficacy and tolerability of FOLFIRINOX in LAPC and MPC and suggest that dose attenuations of irinotecan and bolus fluorouracil improve tolerability without compromising efficacy.

Keywords Pancreatic cancer · FOLFIRINOX · Metastatic pancreatic cancer · Locally advanced pancreatic cancer · Dysarthria

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death in men and women [1]. There were an estimated 43,920 new cases and 37,390 deaths from pancreatic cancer in the United States in 2012, and the 5-year survival for all patients with pancreatic adenocarcinoma is <5 % [2]. The vast majority of patients (80–90 %) present with incurable metastatic or locally advanced unresectable disease. Gemcitabine has been the standard of care for treatment of advanced pancreatic cancer for over a decade based on a randomized trial showing an improvement in the one-year survival with gemcitabine compared to fluorouracil (FU) (18 vs. 2 %, $p = 0.0001$) [3]. Although well tolerated, the efficacy of gemcitabine is marginal, with reported response rates of less than 10 % and median survivals of less than 7 months in patients with metastatic disease. Despite promising phase II trials with gemcitabine-based combinations in advanced pancreatic cancer, the addition of cytotoxic drugs (e.g., FU, capecitabine, oxaliplatin, cisplatin, irinotecan) or targeted agents (bevacizumab, cetuximab, erlotinib) to gemcitabine has yielded no meaningful gains in overall survival in multiple randomized trials comparing gemcitabine doublets to gemcitabine alone, till recently [4–13].

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Conroy et al. [14] first reported impressive efficacy and acceptable tolerability of the combination regimen FOLFIRINOX (oxaliplatin 85 mg/m² over 2 h, followed by irinotecan 180 mg/m² over 90 min and leucovorin 400 mg/m² over 2 h, followed by FU 400 mg/m² bolus and 2,400 mg/m² 46 h continuous infusion) in a phase II study in 46 patients with unresectable pancreatic cancer (11 locally advanced, 35 metastatic). In this preliminary study, there were no toxic deaths, and the confirmed response rate was 26 %, including 4 % complete response rate, and median overall survival was 10.2 months. Subsequently, FOLFIRINOX was compared to gemcitabine in a randomized phase III trial in patients with metastatic pancreatic cancer [15]. This study showed significant improvements in overall survival (11.1 vs. 6.8 mo), progression-free survival (6.4 vs. 3.3 mo) and response rate (31.6 vs. 9.4 %) with FOLFIRINOX compared to gemcitabine. However, FOLFIRINOX was associated with significantly more grade 3 and 4 toxicity than gemcitabine (diarrhea, neutropenia, febrile neutropenia, thrombocytopenia and sensory neuropathy). Based on this study, FOLFIRINOX is considered the most effective regimen for metastatic pancreatic cancer, and it is emerging as the new standard of care in appropriate patients with a good performance status. However, given its toxicities, there has been a reluctance to use FOLFIRINOX in full doses, despite the significant increase in efficacy of this regimen compared to gemcitabine.

It is unknown whether the administration of attenuated doses of FOLFIRINOX compromises its efficacy. Moreover, there is a paucity of data regarding the efficacy of FOLFIRINOX in patients with non-metastatic locally advanced pancreatic cancer. We conducted a retrospective review of patients with metastatic or locally advanced unresectable pancreatic cancer treated with FOLFIRINOX at Yale's Smilow Cancer Center to assess the efficacy and the toxicities of this regimen as it is used in an academic practice with routine dose attenuations.

Methods

Design

We conducted a retrospective review of all patients with locally advanced unresectable and metastatic pancreatic cancer treated with FOLFIRINOX at Yale's Smilow Cancer Center between June 2010 and July 2011. We evaluated patient characteristics, toxicities, response rate (RR), progression-free survival (PFS), and overall survival (OS) based on review of the patients' medical records and imaging studies. Toxicities in the entire Yale cohort (locally advanced and metastatic patients), and patient characteristics and RR in the metastatic cohort, were compared to the FOLFIRINOX-treated group as reported by Conroy et al. [15].

Treatment

Full dose FOLFIRINOX consisted of oxaliplatin 85 mg/m² over 2 h, followed by irinotecan (IRI) 180 mg/m² over 90 min and leucovorin (LV) 400 mg/m² over 2 h, followed by FU 400 mg/m² as a bolus and 2,400 mg/m² as a 46 h continuous infusion. Dose modifications were made at the treating physician's discretion. All patients received peg-filgrastim with the first cycle and subsequent cycles in the absence of severe leukocytosis. Patients routinely received palonosetron, aprepitant, and dexamethasone for emesis prophylaxis.

Assessment

Patients were evaluated for toxicities at the start of each cycle with history, examination, performance status, complete blood count, and metabolic panel. Response assessment imaging was obtained after every 4–6 cycles of treatment. All scans were systematically reviewed by the investigators (KSG, JRT) for response by RECIST.

Duration of treatment and follow-up

Treatment was discontinued at the discretion of the treating physician for unacceptable toxicity, progression of disease, or pursuit of alternative therapies, including surgical resection or radiotherapy for locally advanced disease. Patients were followed for PFS and OS.

Statistics

Toxicities in the entire Yale group were compared with the toxicities in the FOLFIRINOX-treated group as reported by Conroy et al. [15]. One-sample proportion test was used to compare the proportion of grade 3 and 4 adverse events (AEs). Patient characteristics and RR of the Yale metastatic cohort were compared with the FOLFIRINOX-treated group as reported by Conroy et al. [15]. One-sample Wilcoxon signed rank test or Fisher's exact test was used to compare patient characteristics. One-sample proportion test was used to compare the RR in previously untreated metastatic patients. OS and PFS analyses were performed using Kaplan–Meier method. Two patients in the metastatic cohort who had received prior chemotherapy for metastatic disease were excluded from RR and survival analysis.

Results

Patient characteristics

Between June 2010 and July 2011, 35 patients with advanced pancreatic adenocarcinoma were treated with

FOLFIRINOX at the Yale Smilow Cancer Center, including 16 with locally advanced unresectable disease and 19 with metastatic disease. The demographics and disease characteristics are shown in Table 1. Compared to the series reported by Conroy et al. [15] in previously untreated patients with metastatic disease who received FOLFIRINOX, more patients with metastatic disease in our cohort were female ($p = 0.006$) and had ECOG PS of 0 ($p = 0.003$). In our 19 patients with metastatic disease, 2 had received prior adjuvant chemotherapy, 1 had received prior neoadjuvant chemoradiotherapy, and 2 had received prior chemotherapy for metastatic disease.

Dose modifications and supportive care

Dose modifications were at the discretion of the treating physician. Only 6 of 35 patients received full doses of each drug of FOLFIRINOX with the first cycle. In the remaining 29 patients, dose attenuations with the first cycle were as follows: IRI was reduced in 27 and omitted in 1, OX was reduced in 10, bolus FU was reduced in 9 and omitted in 7, LV was decreased in 11, infusional FU was reduced in 3. The median number of cycles received was 11 (range 1–28). The median relative doses of each drug (in comparison with the median relative doses in FOLFIRINOX-treated patients reported by Conroy et al. [15]) were as follows: OX 90 % (vs. 78 %), IRI 64 % (vs. 81 %), bolus FU 66 % (vs. 82 %), and infusional FU 100 % (vs. 82 %). 34 of 35 patients received peg-filgrastim with the first cycle and subsequent cycles, except in the event of severe leukocytosis, at the discretion of the treating physician.

Efficacy

Response

Response rates in patients with locally advanced and metastatic disease are shown in Table 2. Two of 19 patients with metastatic disease were excluded from the analysis, as they had received prior chemotherapy for metastatic

disease. The RR (CR + PR) in the entire group (locally advanced and metastatic) was 48 %, with 1 CR and 15 PR in 33 patients. In patients with metastatic disease, the RR was 47 % and did not differ significantly from the RR of 32 % reported by Conroy et al. in FOLFIRINOX-treated patients ($p = 0.19$). In patients with locally advanced disease, the RR was 50 %, and two patients were able to undergo resection after 4 and 6 cycles. One of these patients had a near pathologic complete response with 2 mm of residual tumor.

Progression-free and overall survival

The survival data are shown in Table 3 and Fig. 1. For the entire cohort of patients (locally advanced and metastatic), the median PFS was 16.1 months, and the median OS has not been reached.

In patients with metastatic disease, the median PFS and OS were 9.9 and 11.2 months, respectively. The PFS in the metastatic cohort at 6 and 12 months was 76 and 35 %, respectively, and the OS at 6 and 12 months was 82 and 50 %, respectively. By comparison, the OS at 6 and 12 months was 75.9 and 48.4 %, respectively, in the FOLFIRINOX-treated patients as reported by Conroy et al. [15].

In patients with locally advanced disease, the median PFS and OS have not been reached. The PFS for locally advanced disease at 6 and 12 months was 94 and 77 %, respectively, and the OS at 6 and 12 months was 94 and 83 %, respectively.

Adverse events

Treatment-related grade 3 and 4 toxicities are summarized in Table 4. There were no toxic deaths attributable to FOLFIRINOX. The incidence of grade 3 or 4 fatigue (5.7 vs. 23.6 %, $p = 0.009$) and neutropenia (11.4 vs. 45.7 %, $p < 0.0001$) was significantly decreased in our cohort compared to the FOLFIRINOX-treated patients as reported

Table 1 Patient demographics and characteristics

Characteristic	Total (<i>n</i> = 35)	Locally advanced (<i>n</i> = 16)	Metastatic (<i>n</i> = 19)	Historical data ¹⁵ (<i>n</i> = 171)	<i>p</i> value*
Age	61 (48–77)	60 (51–77)	62 (48–76)	61 (25–76)	0.81 ⁺
Male	13 (37 %)	8 (50 %)	5 (26 %)	106 (62 %)	0.006 ⁺⁺
Female	22 (63 %)	8 (50 %)	14 (74 %)	65 (38 %)	
ECOG PS					
0	24 (69 %)	10 (62 %)	14 (74 %)	64 (37 %)	0.003 ⁺⁺
1	11 (31 %)	6 (37 %)	5 (26 %)	106 (62 %)	
Prior therapy	5 (14 %)	0 (0 %)	5 (26 %)	0 (0 %)	
Tumor location					
Head	20 (57 %)	8 (50 %)	12 (63 %)	67 (39 %)	0.05 ⁺⁺
Other	15 (43 %)	8 (50 %)	7 (37 %)	104 (61 %)	

* Comparison between the Yale metastatic group and historical control group of FOLFIRINOX-treated patients reported by Conroy et al. [15]

⁺ One-sample Wilcoxon signed rank test

⁺⁺ Fisher's exact test

Table 2 Objective response

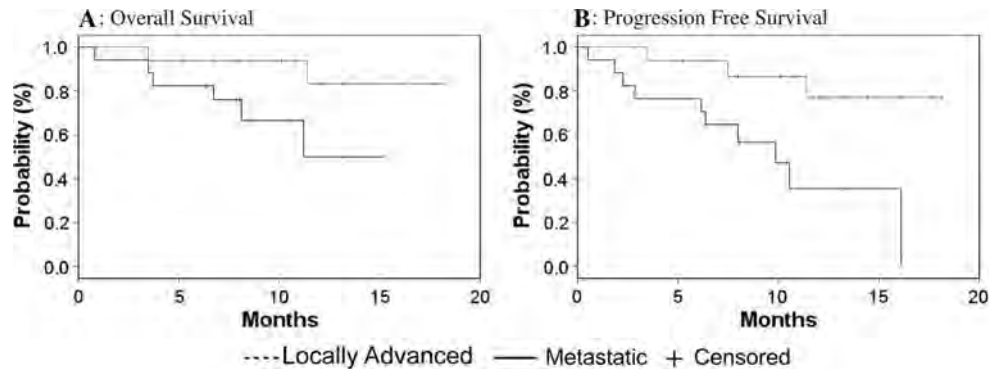
	Total (n = 33)	Locally advanced (n = 16)	Metastatic (n = 17)	Historical data ¹⁵ (n = 171)	p value*
CR	1 (3 %)	1 (6 %)	0 (0 %)	1 (0.6 %)	
PR	15 (45 %)	7 (44 %)	8 (47 %)	53 (31 %)	
SD	13 (39 %)	7 (44 %)	6 (35 %)	66 (39 %)	
PD	2 (6 %)	0 (0 %)	2 (12 %)	26 (15 %)	
CR + PR	16 (48 %)	8 (50 %)	8 (47 %)	54 (32 %)	0.19
CR + PR + SD	29 (88 %)	15 (94 %)	14 (82 %)	120 (70 %)	0.43

* Comparison between the Yale metastatic group and historical control group of FOLFIRINOX-treated patients reported by Conroy et al. [15]. p values are based on one-sample proportion test

Table 3 Survival

	Overall survival			Progression-free survival		
	Median (mos)	6-month	12-month	Median (mos)	6-month	12-month
All patients (n = 33)	Not reached	88 %	68 %	16.1	85 %	57 %
Metastatic (n = 17)	11.2	82 %	50 %	9.9	76 %	35 %
Locally advanced (n = 16)	Not reached	94 %	83 %	Not reached	94 %	77 %

Fig. 1 Kaplan–Meier survival estimates of overall survival (a) and progression-free survival (b) of patients with locally advanced (dotted line) and metastatic (solid line) pancreatic cancer



by Conroy et al. [15]. There was a non-significant trend toward a lower incidence of febrile neutropenia, anemia, thrombocytopenia, vomiting, diarrhea, and neuropathy compared to the FOLFIRINOX-treated patients as reported by Conroy et al. [15]. Grade 3 or 4 diarrhea in our patient population was just 2.9 % compared to 12.7 % in the FOLFIRINOX-treated patients as reported by Conroy et al. [15].

In our study, there were nine cases of acute onset of dysarthria and other neurological symptoms during the FOLFIRINOX infusion. These symptoms included dysarthric speech, facial or perioral paresthesias, leg cramps, ataxia, and blepharospasm. In all cases, the onset of these neurological symptoms was temporally associated with the irinotecan infusion. The symptoms remitted with interruption of the irinotecan infusion, and in some cases, recurred with re-challenge. In all cases, the symptoms resolved completely without specific intervention other than transient interruption of the irinotecan infusion and/or

administration of anticholinergic agents (atropine and/or diphenhydramine). The first two patients in whom these symptoms developed were hospitalized for neurological work up to rule out a cerebral vascular event; subsequent patients were managed as out-patients in the infusion center. Dose reduction of irinotecan and/or pre-medication with anticholinergics, at the discretion of the treating physician, prevented or mitigated the severity of these neurologic symptoms in subsequent cycles in all patients.

Discussion

Our single institution retrospective study validates the efficacy of FOLFIRINOX in unselected patients with locally advanced and metastatic pancreatic cancer. The majority of the patients treated at our institution received attenuated doses of FOLFIRINOX with the first and subsequent cycles of treatment, and the median relative doses

Table 4 Adverse events

Grade 3/4 event	Yale (<i>n</i> = 35)	Historical data ¹⁵ (<i>n</i> = 171)	<i>p</i> value*
<i>Hematologic</i>			
Neutropenia	4 (11.4 %)	75/164 (45.7 %)	<0.0001
Febrile neutropenia	1 (2.9 %)	9/166 (5.4 %)	1.0
Thrombocytopenia	1 (2.9 %)	15/165 (9.1 %)	0.37
Anemia	0 (0 %)	13/166 (7.8 %)	0.11
<i>Non-hematologic</i>			
Fatigue	2 (5.7 %)	39/165 (23.6 %)	0.009
Diarrhea	1 (2.9 %)	21/165 (12.7 %)	0.12
Vomiting	1 (2.9 %)	24/166 (14.5 %)	0.05
Neuropathy	0 (0 %)	15/166 (9.0 %)	0.07

* Comparison between the Yale group and historical control group of FOLFIRINOX-treated patients reported by Conroy et al. [15]. *p* values are based on one-sample proportion test

of IRI and bolus FU were lower than those reported in the FOLFIRINOX-treated group reported by Conroy et al. [15]. Nonetheless, our findings suggest that the efficacy of FOLFIRINOX was not compromised by these dose modifications. The RR of 47 % in our patients with metastatic disease was not significantly different from the RR of 32 % in the FOLFIRINOX-treated patients as reported by Conroy et al. [15]. Moreover, the observed PFS and OS at 6 and 12 months, as well as the median OS and PFS, in our patients with metastatic disease were also comparable to the survivals reported by Conroy et al. [15] in the FOLFIRINOX-treated patients.

Although FOLFIRINOX is associated with a significant increase in response rate and overall survival in metastatic pancreatic cancer compared to gemcitabine, the toxicities of FOLFIRINOX have tempered enthusiasm for its use in full doses in community and academic centers [15]. Our study suggests that incorporation of modest dose attenuations of IRI and bolus FU in the majority of patients, in conjunction with routine use of growth factor support with the first and subsequent cycles, is associated with less toxicity than observed in the FOLFIRINOX-treated patients reported by Conroy et al. [15]. We observed a significant decrease in the incidence of grade 3 or 4 fatigue and neutropenia, and a trend toward decreased incidence of febrile neutropenia, anemia, thrombocytopenia, diarrhea, vomiting, and neuropathy in our cohort compared to the FOLFIRINOX-treated patients reported by Conroy et al. [15]. The improved tolerability of FOLFIRINOX in our institution’s cohort of patients may be related to the dose modifications, routine use of growth factor support, or the use of aggressive anti-emetic and anti-diarrheal regimens. In addition, a higher percentage of our patients had an ECOG PS of 0 compared to the FOLFIRINOX-treated patients reported by Conroy et al. [15]. Interestingly, 57 % of our patients had carcinoma of the head of the pancreas, compared to 39 % of patients reported by Conroy et al. Although 31 % of our patients had biliary stents for obstruction, we observed only one case of cholangitis.

The optimum treatment of locally advanced unresectable pancreatic cancer remains uncertain. Current therapeutic options include chemoradiation or chemotherapy alone. Meta-analyses comparing chemotherapy with chemoradiation showed no survival benefit and increased toxicity for chemoradiotherapy compared to chemotherapy [16–18]. The combination of gemcitabine and oxaliplatin was compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer in the GERGOR/GISCAD randomized trial. Despite an increased RR in locally advanced disease with gemcitabine/oxaliplatin compared to gemcitabine (27 vs. 14 %), the overall survival was identical at 10.3 mo in both arms [7]. In a subsequent randomized ECOG trial comparing conventional gemcitabine, gemcitabine fixed-dose rate (FDR) infusion, and gemcitabine/oxaliplatin in advanced pancreatic cancer, there was no difference in RR, PFS, or OS between any of the regimens, and the median survival was just 9.2 months in locally advanced disease [8].

Although FOLFIRINOX has superior efficacy compared to gemcitabine in patients with metastatic pancreatic cancer, there are limited data regarding its efficacy and tolerability in locally advanced pancreatic cancer. In the initial phase II trial of FOLFIRINOX, only 11 patients had locally advanced disease, and in these patients, the RR was 27 % and median OS was 15.7 mos [14]. In our cohort of 16 patients with locally advanced pancreatic cancer treated with FOLFIRINOX, we observed a response rate of 50 % and a disease control rate of 94 %, confirming impressive efficacy of FOLFIRINOX in locally advanced disease. The RR in our cohort of locally advanced pancreatic cancer is higher than that reported for gemcitabine-based regimens and is similar to the RR reported by Conroy et al. [15] in FOLFIRINOX-treated patients with metastatic disease. The PFS for locally advanced disease at 6 and 12 months was 94 and 77 %, respectively, and the OS at 6 and 12 month was 94 and 83 %, respectively. Two of our 16 patients with locally advanced disease were able to undergo resection, and one patient had near complete

pathological response. Our findings suggest that the efficacy and tolerability of FOLFIRINOX in locally advanced pancreatic cancer is similar to its efficacy in the metastatic setting and support the use of FOLFIRINOX as initial therapy in patients with locally advanced or borderline disease.

We report nine cases of acute onset of dysarthria and other neurological symptoms (facial or perioral paresthesias, leg cramps, ataxia, and blepharospasm) during the FOLFIRINOX infusion. The onset of these symptoms was temporally associated with the irinotecan infusion. In all cases, the symptoms resolved completely without specific intervention other than transient interruption of the irinotecan infusion and/or administration of anticholinergic agents (atropine or diphenhydramine). In some cases, the symptoms recurred with re-initiation of the irinotecan infusion, but resolved with administration of anticholinergic agents. Neurotoxic effects of irinotecan are uncommon, and only four cases have been reported in the literature [19–22]. The mechanism by which CNS toxicity occurs after irinotecan infusion is not well understood. Harel et al. [23] proposed that irinotecan causes increased cholinergic activity by binding to the active site of acetylcholinesterase causing its functional inhibition. Cholinergic receptors are found more in the brainstem nuclei and using cholinergic agents result in a surge of hypoglossal nerve activity [24, 25], which might explain the dysarthria associated with irinotecan toxicity. This mechanism could be related to cholinergic oversensitivity of the neurons in the hypoglossal nerve nucleus. Atropine has not been shown to prevent dysarthria, and all the reported cases showed that these symptoms were reversible and severity did not worsen upon re-challenging with irinotecan [26]. Since oxaliplatin is routinely administered prior to irinotecan in the FOLFIRINOX regimen, we speculate that oxaliplatin may enhance the neurotoxic effects of irinotecan, thereby increasing the incidence of this rare side effect of irinotecan.

Conclusions

In this single institution retrospective study, the routine use of modest dose attenuations of FOLFIRINOX, in conjunction with growth factor support, was associated with improved tolerability compared to full dose FOLFIRINOX as reported by Conroy et al. Our findings suggest that these modest dose attenuations do not reduce the efficacy of FOLFIRINOX in metastatic pancreatic cancer patients. Moreover, the efficacy of FOLFIRINOX in locally advanced disease was comparable to its efficacy in metastatic disease. Given the number of patients in our series and the limitations of a retrospective study, our findings require further substantiation. Prospective trials are needed to validate the efficacy and tolerability of modifications of

FOLFIRINOX in metastatic pancreatic cancer. In patients with locally advanced and borderline disease, we need to better define the activity of FOLFIRINOX and its role and safety in the neoadjuvant setting.

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Conflict of interest None.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics. *CA Cancer J Clin.* 2010;60(5):277–300. doi:[10.3322/caac.20073](https://doi.org/10.3322/caac.20073).
2. Siegel R, Naishadham D, Jemal A. Cancer statistics. *CA Cancer J Clin.* 2012;62(1):10–29. doi:[10.3322/caac.20138](https://doi.org/10.3322/caac.20138).
3. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol.* 1997;15(6):2403–13.
4. Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson AB 3rd. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. *J Clin Oncol.* 2002;20(15):3270–5.
5. Heinemann V, Boeck S, Hinke A, Labianca R, Louvet C. Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. *BMC Cancer.* 2008;8:82. doi:[10.1186/1471-2407-8-82](https://doi.org/10.1186/1471-2407-8-82).
6. Herrmann R, Bodoky G, Ruhstaller T, Glimelius B, Bajetta E, Schuller J, Saletti P, Bauer J, Figer A, Pestalozzi B, Kohne CH, Mingrone W, Stemmer SM, Tamas K, Kornek GV, Koeberle D, Cina S, Bernhard J, Dietrich D, Scheithauer W. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. *J Clin Oncol.* 2007;25(16):2212–7. doi:[10.1200/JCO.2006.09.0886](https://doi.org/10.1200/JCO.2006.09.0886).
7. Louvet C, Labianca R, Hammel P, Lledo G, Zampino MG, Andre T, Zaniboni A, Ducreux M, Aitini E, Taieb J, Faroux R, Lepere C, de Gramont A. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol.* 2005;23(15):3509–16. doi:[10.1200/JCO.2005.06.023](https://doi.org/10.1200/JCO.2005.06.023).
8. Poplin E, Feng Y, Berlin J, Rothenberg ML, Hochster H, Mitchell E, Alberts S, O'Dwyer P, Haller D, Catalano P, Cella D, Benson AB 3rd. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-min infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol.* 2009;27(23):3778–85. doi:[10.1200/JCO.2008.20.9007](https://doi.org/10.1200/JCO.2008.20.9007).
9. Heinemann V, Quietzsch D, Gieseler F, Gonnermann M, Schonekas H, Rost A, Neuhaus H, Haag C, Clemens M, Heinrich B, Vehling-Kaiser U, Fuchs M, Fleckenstein D, Gesierich W, Uthgenannt D, Einsele H, Holstege A, Hinke A, Schalhorn A, Wilkowski R. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol.* 2006;24(24):3946–52. doi:[10.1200/JCO.2005.05.1490](https://doi.org/10.1200/JCO.2005.05.1490).

10. Rocha Lima CM, Green MR, Rotche R, Miller WH Jr, Jeffrey GM, Cisar LA, Morganti A, Orlando N, Gruia G, Miller LL. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol*. 2004;22(18):3776–83. doi:[10.1200/JCO.2004.12.08222/18/3776](https://doi.org/10.1200/JCO.2004.12.08222/18/3776).
11. Kindler HL, Niedzwiecki D, Hollis D, Sutherland S, Schrag D, Hurwitz H, Innocenti F, Mulcahy MF, O'Reilly E, Wozniak TF, Picus J, Bhargava P, Mayer RJ, Schilsky RL, Goldberg RM. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). *J Clin Oncol*. 2010;28(22):3617–22. doi:[10.1200/JCO.2010.28.1386](https://doi.org/10.1200/JCO.2010.28.1386).
12. Philip PA, Benedetti J, Corless CL, Wong R, O'Reilly EM, Flynn PJ, Rowland KM, Atkins JN, Mirtsching BC, Rivkin SE, Khorana AA, Goldman B, Fenoglio-Preiser CM, Abbruzzese JL, Blanke CD. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. *J Clin Oncol*. 2010;28(22):3605–10. doi:[10.1200/JCO.2009.25.7550](https://doi.org/10.1200/JCO.2009.25.7550).
13. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, Campos D, Lim R, Ding K, Clark G, Voskoglou-Nomikos T, Ptasynski M, Parulekar W. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 2007;25(15):1960–6. doi:[10.1200/JCO.2006.07.9525](https://doi.org/10.1200/JCO.2006.07.9525).
14. Conroy T, Paillot B, Francois E, Bugat R, Jacob JH, Stein U, Nasca S, Metges JP, Rixe O, Michel P, Magherini E, Hua A, Deplanque G. Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer—a Groupe Tumeurs Digestives of the Federation Nationale des Centres de Lutte Contre le Cancer study. *J Clin Oncol*. 2005;23(6):1228–36. doi:[10.1200/JCO.2005.06.050](https://doi.org/10.1200/JCO.2005.06.050).
15. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardiere C, Bennouna J, Bachet JB, Khemissa-Akouz F, Pere-Verge D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364(19):1817–25. doi:[10.1056/NEJMoa1011923](https://doi.org/10.1056/NEJMoa1011923).
16. Huguet F, Girard N, Guerche CS, Hennequin C, Mornex F, Azria D. Chemoradiotherapy in the management of locally advanced pancreatic carcinoma: a qualitative systematic review. *J Clin Oncol*. 2009;27(13):2269–77. doi:[10.1200/JCO.2008.19.7921](https://doi.org/10.1200/JCO.2008.19.7921).
17. Moertel CG, Frytak S, Hahn RG, O'Connell MJ, Reitemeier RJ, Rubin J, Schutt AJ, Weiland LH, Childs DS, Holbrook MA, Lavin PT, Livstone E, Spiro H, Knowlton A, Kalser M, Barkin J, Lessner H, Mann-Kaplan R, Rammig K, Douglas HO Jr, Thomas P, Nave H, Bateman J, Lokich J, Brooks J, Chaffey J, Corson JM, Zamcheck N, Novak JW. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6,000 rads) radiation alone, moderate dose radiation (4,000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: the Gastrointestinal Tumor Study Group. *Cancer*. 1981;48(8):1705–10.
18. Sultana A, Smith CT, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. *J Clin Oncol*. 2007;25(18):2607–15. doi:[10.1200/JCO.2006.09.2551](https://doi.org/10.1200/JCO.2006.09.2551).
19. De Marco S, Squilloni E, Vigna L, Bertagnolio MF, Sternberg CN. Irinotecan chemotherapy associated with transient dysarthria and aphasia. *Ann Oncol*. 2004;15(7):1147–8. doi:[10.1093/annonc/mdh27715/7/1147](https://doi.org/10.1093/annonc/mdh27715/7/1147).
20. Baz DV, Bofill JS, Nogueira JA. Irinotecan-induced dysarthria. *J Natl Cancer Inst*. 2001;93(18):1419–20.
21. Hamberg P, De Jong FA, Brandsma D, Verweij J, Sleijfer S. Irinotecan-induced central nervous system toxicity. Report on two cases and review of the literature. *Acta Oncol*. 2008;47(5):974–8. doi:[10.1080/02841860701666089](https://doi.org/10.1080/02841860701666089).
22. Sevilla Garcia I, Rueda A, Alba E. Irinotecan-induced central nervous system toxicity: a case report. *J Natl Cancer Inst*. 1999;91(7):647.
23. Harel M, Hyatt JL, Brumshtein B, Morton CL, Yoon KJ, Wadkins RM, Silman I, Sussman JL, Potter PM. The crystal structure of the complex of the anticancer prodrug 7-ethyl-10-[4-(1-piperidino)-1-piperidino]-carbonyloxycamptothecin (CPT-11) with *Torpedo californica* acetylcholinesterase provides a molecular explanation for its cholinergic action. *Mol Pharmacol*. 2005;67(6):1874–81. doi:[10.1124/mol.104.009944](https://doi.org/10.1124/mol.104.009944).
24. Cortes R, Probst A, Palacios JM. Quantitative light microscopic autoradiographic localization of cholinergic muscarinic receptors in the human brain: brainstem. *Neuroscience*. 1984;12(4):1003–26.
25. Haxhiu MA, Mitra J, van Lunteren E, Bruce EN, Cherniack NS. Hypoglossal and phrenic responses to cholinergic agents applied to ventral medullary surface. *Am J Physiol*. 1984;247(6 Pt 2):R939–44.
26. Dressel AJ, van der Mijl JC, Aalders IJ, Rinkel RN, van der Vliet HJ. Irinotecan-induced dysarthria. *Case Rep Oncol*. 2012;5(1):47–51. doi:[10.1159/000336156](https://doi.org/10.1159/000336156).

Appendix GURNEY01

Short Communication

How to calculate the dose of chemotherapy

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Body surface area-dosing does not account for the complex processes of cytotoxic drug elimination. This leads to an unpredictable variation in effect. Overdosing is easily recognised but it is possible that unrecognised underdosing is more common and may occur in 30% or more of patients receiving standard regimen. Those patients who are inadvertently underdosed are at risk of a significantly reduced anticancer effect. Using published data, it can be calculated that there is an almost 20% relative reduction in survival for women receiving adjuvant chemotherapy for breast cancer as a result of unrecognised underdosing. Similarly, the cure rate of cisplatin-based chemotherapy for advanced testicular cancer may be reduced by as much as 10%. The inaccuracy of body surface area-dosing is more than an inconvenience and it is important that methods for more accurate dose calculation are determined, based on the known drug elimination processes for cytotoxic chemotherapy. Twelve rules for dose calculation of chemotherapy are given that can be used as a guideline until better dose-calculation methods become available. Consideration should be given to using fixed dose guidelines independent of body surface area and based on drug elimination capability, both as a starting dose and for dose adjustment, which may have accuracy, safety and financial advantages.

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Keywords: dose calculation; under-dose; body surface area

Despite the recent advances in anticancer treatment and the promise of novel targeted therapies, it is likely that cytotoxic chemotherapy will continue to be used for the next few decades. It is now recognised that our current method of dose calculation for chemotherapy using body surface area (BSA) is inaccurate (Gurney, 1996, 1998; Ratain, 1998). This method does not account for the marked inter-patient variation in drug handling that is known to exist for these drugs so that drug effects such as toxicity are also highly variable and therefore unpredictable. One consequence is unexpected underdosing which leads to reduced effectiveness of chemotherapy. However, until there is a better method, BSA-dosing will prevail since there has been over 40 years of experience with this method and 'old habits die hard'. The following discussion will remind the clinician of the inaccuracies of this system and will suggest guidelines for dose calculation that encourages consideration of important parameters other than BSA alone.

To calculate dose accurately drug elimination needs to be understood. Typically there is a 4–10-fold variation in cytotoxic drug clearance between individuals due to differing activity of drug elimination processes related to genetic and environmental factors (Gurney, 1996). For example, the activity of cytochrome P450 (CYP) 3A4/5, the major oxidising enzymes for many cytotoxic drugs varies by as much as 50-fold (Wrighton *et al*, 1996). A common single-nucleotide polymorphism (SNP) or CYP3A5 has recently been identified and others are being searched for (Kuehl *et al*, 2001). In addition many drugs and disease states are known to inhibit or induce CYP activity further adding to this variation (George *et al*, 1996). Another example is the eight-fold variation in dihydropyrimidine dehydrogenase (DPD) activity, the enzyme

that catabolises 5FU (Etienne *et al*, 1994). Less is known about the variation in other critical hepatic elimination processes such as active biliary excretion by multidrug resistance gene 1 (MDR1), multidrug resistance-associated protein 2 (MRP2) and the other ATP binding cassette (ABC) family of efflux pumps, although some polymorphisms have been identified (Tanabe *et al*, 2001). A number of SNPs have also recently been identified for the steroid and xenobiotic receptor (SXR), a common-pathway receptor which transcriptionally activates a number of the drug elimination genes such as CYP3A4, MRP2 and MDR1 (Zhang *et al*, 2001). Variation in renal function is more easily identified but none of these complex processes are accounted for when BSA alone is used to calculate drug dose.

THE PROBLEM OF UNDERDOSING

It is clear that for most cancers there is a plateau in the dose–response curve for cytotoxic chemotherapy. Increasing the dose above a standard dose will increase toxicity, but does not improve anti-tumour effect (Gurney *et al*, 1993; Stadtmauer *et al*, 2000). High-dose chemotherapy is now largely reserved for acute leukaemia and aggressive lymphomas in relapse. However, the dose intensity studies from the last two decades have shown that anti cancer effect is substantially reduced if the dose of drug is intentionally decreased below the standard. What has not been recognised is that a significant proportion of patients may be *inadvertently* underdosed because of our inaccurate dose–calculation methods, which may cause a reduced cure or other effect.

The dose of a new drug is conventionally determined in a phase I study and then adjusted after more widespread use. The end point of this process is prevention of toxicity rather than identifying the dose for best anti-tumour effect. One consequence of this, coupled with the inaccuracy of BSA-dosing, is that significant underdosing becomes intrinsic to our system of dose determina-

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tion. Figure 1 illustrates the scheme of a phase I study for a drug with linear pharmacokinetics. The horizontal lines represent the variation in systemic exposure at various dose levels. At dose level 3, those patients with lower drug elimination capability develop dose-limiting toxicity and subsequently that dose level is defined as the maximum tolerated dose. Dose level 2 is recommended for phase II studies since it causes tolerable toxicity in all patients. However, due to the variation in drug handling, a proportion of patients will be relatively underdosed since they are more capable of eliminating the drug. This means the wide distribution of systemic exposure is skewed towards the ineffective range when dose is calculated using BSA. Evidence for this effect can be found in a recent study by Gaemelin *et al* (1999). This group had defined the optimum 5FU plasma concentration with a regimen using 5FU in a dose of 1300 mg m² infused over 8 h every week. For a group of 81 patients treated with dose calculated using BSA, 80% of patients were found to have an ineffective 5FU plasma concentration after the first dose.

What other evidence is available to indicate that underdosing occurs with the current dose calculation method? Here the problem is in defining and identifying underdosing. Can the lack of effect on normal tissue (i.e. toxicity) be used to identify a lack of effect in neoplastic tissue? For this to be tenable a toxicity-response relationship must be shown for cytotoxic chemotherapy. There is a wealth of information regarding dose–toxicity and dose–response relationships but very little information is available in the literature examining the relationship between toxicity and response (Gurney *et al*, 1993). Three studies from the 1970s and 80s purport a relationship between lack of myelosuppression and lack of anti-tumour effect in osteosarcoma and multiple myeloma (Cortes *et al*, 1974;

McIntyre *et al*, 1978; Carpenter *et al*, 1982). However, a firm relationship cannot be claimed given the low patient numbers and the technique of analysis of these studies.

More recently, some studies have illustrated a toxicity-response relationship for breast cancer, testis cancer, ovarian cancer and lymphoma (Table 1) (Rankin *et al*, 1992; Horwich *et al*, 1997; Poikonen *et al*, 1999). A randomised MRC study of combination chemotherapy in advanced testicular cancer showed a significantly higher relapse rate in patients receiving carboplatin who failed to develop myelosuppression. There was a similar relationship shown for patients receiving cisplatin. Relapse rate for the cisplatin containing regimen was 11% for patients with a nadir white cell count (WCC) of over 2.0×10^9 per litre compared with 4% for patients whose WCC fell below 2.0×10^9 per litre after chemotherapy. Although this difference was not statistically significant, inadvertent underdosing may be an issue for cisplatin as well as carboplatin-containing regimen in the treatment of testicular cancer. These studies show a significantly worse anti-tumour effect for those patients who failed to develop myelosuppression after treatment compared to those who did. It is important that this relationship is examined more fully in other cancer types. This can be done by re-analysis of previous studies where nadir blood counts have been recorded in the majority of patients. A recent randomised study by the Australian Lymphoma and Leukaemia Group comparing high dose cyclophosphamide, epirubicin, vincristine and prednisolone (CEOP) with standard dose CEOP, showed that those patients who did not experience a nadir neutrophil count of $< 1.0 \times 10^9$ per litre, had a statistically inferior progression free survival (Gurney *et al*, manuscript in preparation).

If lack of myelosuppression is accepted as an indication of underdosing, the frequency of this event can then be determined. Table 2 is a selection of trials where the frequency and timing of nadir blood counts have been adequately recorded. A substantial percentage of patients (30 to 75%) receiving commonly used chemotherapy regimen have 'inadequate' myelosuppression and may be underdosed.

THE SIGNIFICANCE OF UNDERDOSING

The possible significance of the underdosing is outlined in Table 3. Calculation of published data from studies using adjuvant cyclophosphamide, doxorubicin and 5FU (CAF) for node positive breast cancer show that BSA-based dosing may lead to almost a 20% relative reduction in survival in this setting (Budman *et al*, 1998; Early Breast Cancer Trialists' Collaborative Group, 1998; Silber *et al*, 1998). This impact is equivalent to the benefit from the use of adjuvant chemotherapy in node negative breast cancer, or the addition of paclitaxel to the CAF regimen in node positive breast cancer. Similarly, BSA-based dosing may reduce the cure rate of intermediate prognosis testis cancer by almost 10% compared to a dosing method that prevents underdosing (Samson *et al*, 1984; Horwich *et al*, 1997). Clearly, if these calculations are

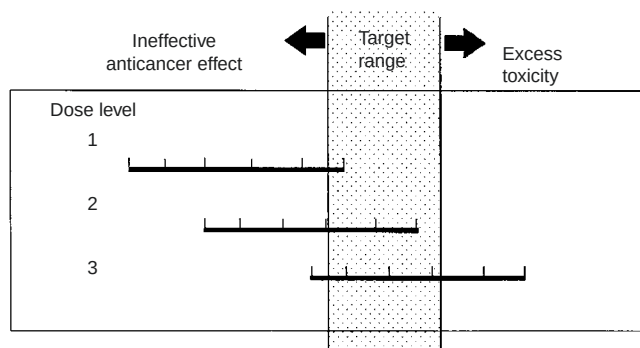


Figure 1 Hypothetical phase I study of a drug with linear pharmacokinetics. Horizontal bars represent interpatient variation in systemic exposure. Each vertical tick mark represents an individual patient on the study. Dose level 3 would be considered the MTD and dose level 2 would be recommended for phase II study despite the majority of patients on that dose level having a systemic exposure in the sub-therapeutic range.

Table 1 Relationship between myelosuppression and anticancer effect

Reference	Tumour type	Outcome
Carpenter <i>et al</i> , 1982	Stage 2 breast cancer randomised between melphalan or CMF	In patients with 1 to 3 nodes, a nadir WCC of $< 3 \times 10^9$ per litre was significant predictor of disease free survival in multivariate analysis
Poikonen <i>et al</i> , 1999	Stage 2 breast cancer treated with CMF	Low nadir leukocyte associated with longer distant disease free survival.
Horwich <i>et al</i> , 1997	Testis cancer treated with carboplatin, etoposide and bleomycin	Patients with nadir WCC $< 2 \times 10^9$ per litre and/or platelets $< 90 \times 10^9$ per litre had lower relapse rate. 14% vs 28%, $P=0.04$
Rankin <i>et al</i> , 1992	Advanced ovarian cancer. Carboplatin plus chlorambucil vs carboplatin	Worse progression-free survival for patients who had grade 0 WCC nadir ($P<0.001$)
Gurney <i>et al</i> , (unpublished)	Aggressive lymphoma treated with CEOP	Worse progression free survival for patients with neutrophil count nadir of $> 1 \times 10^9$ per litre ($P=0.04$)

CMF=cyclophosphamide, methotrexate, 5FU. CAF=cyclophosphamide, doxorubicin, 5FU. CEOP=cyclophosphamide, epirubicin, vincristine, prednisolone.

Table 2 Lack of myelosuppression from standard chemotherapy regimen

Reference	Tumour type	Nadir myelosuppression
Horwich <i>et al</i> , 1997	Testis cancer treated with carboplatin or cisplatin and etoposide, bleomycin	7% of BEP and 65 % of CEB had nadir WCC > 2.0×10^9 per litre
Rankin <i>et al</i> , 1992	Carboplatin (dosed on BSA) with or without chlorambucil for advanced ovarian cancer	29.4% of patients had nadir WCC > 4×10^9 per litre
Budman <i>et al</i> , 1998	Adjuvant CAF for breast cancer	44% of patients had nadir WCC > 2.0×10^9 per litre
Silber <i>et al</i> , 1998	Adjuvant CAF or CMF for breast cancer	50% had nadir neutrophil count > 1.0×10^9 per litre
Bishop <i>et al</i> , 1999	Advanced breast cancer treated with CMF or paclitaxel	37% had nadir neutrophil count > 1.5×10^9 per litre
Ratain <i>et al</i> , 1991	Randomised study of standard vs individualised dose of etoposide by 72 h infusion	60% of patients on standard arm had nadir WCC of > 2.0×10^9 per litre
Hovgaard and Nissen, 1992	CHOP for lymphoma. 127 historical controls.	50% of patients had nadir WCC > 2.0×10^9 per litre

CMF=cyclophosphamide, methotrexate, 5FU. CAF=cyclophosphamide, doxorubicin, 5FU. BEP= bleomycin, etoposide, cisplatin. CEB=carboplatin, etoposide, bleomycin. CHOP=cyclophosphamide, doxorubicin, vincristine, prednisolone.

Table 3

Impact of inadvertent underdosing on adjuvant chemotherapy for stage 2 breast cancer

1. Halving the dose of CAF causes a reduction in the 5-year survival from 79 to 72% (absolute reduction=7%) (Budman *et al*, 1998)
 2. In 50% of patients receiving CAF as adjuvant treatment for breast cancer, the nadir neutrophil count will not fall below 1.0×10^9 per litre. (Silber *et al*, 1998)
 3. There is an absolute survival benefit of 12% for patients less than age of 50 years receiving chemotherapy for node positive breast cancer (Early Breast Cancer Trialists' Collaborative Group, 1998)
- If (conservatively) 30% of patients receiving CAF for stage 2 breast cancer are underdosed because of conventional dosing, absolute reduction in 5-year survival may be 30 of 7%=2.1%, which is a 17.5% relative reduction in survival.

Impact of inadvertent underdosing on chemotherapy for advanced testis cancer

1. A significant reduction in the cisplatin dose (120 to 75 mg m^{-2}) in the PVB regimen causes a reduction in the 3-year survival from 84 to 60% (absolute reduction=24%) (Samson *et al*, 1984)
 2. In 75% of patients receiving BEP for treatment of advanced testis cancer, the nadir white cell will not fall below 2.0×10^9 per litre. (Horwich *et al*, 1997)
 3. The disease-free survival for BEP is 80% at 5 year (intermediate prognosis) (International Germ Cell Consensus Classification, 1997)
- If (conservatively) 30% of patients receiving chemotherapy for advanced testis cancer are underdosed because of conventional dosing, reduction in long term disease free survival may be 30 of 24%=7.2%, which is a 9% relative reduction in cure rate.

accurate, we can no longer tolerate the inaccuracies of BSA dosing as of minor consequence. It is important that more accurate calculation methods are developed. Another obvious bonus of an accurate dose calculation scheme is prevention of toxicity from overdosing.

PREVENTION OF UNDERDOSING

One popular method of dose individualisation is to adjust subsequent doses of chemotherapy based on the level of myelosuppression eventually avoiding overdosing and underdosing – so called ‘toxicity-adjusting dosing’ (Gurney, 1996). A Swedish group has adopted this approach in the adjuvant treatment of breast cancer (Berch *et al*, 2000). Using the 5FU, epirubicin and cyclophosphamide (FEC) regimen, dose adjustments were made on each cycle to ensure a target level of myelosuppression. After a number of dose adjustments this method of individualising dose gave a three-fold interpatient range of cyclophosphamide dose (450 to 1800 mg m^{-2}) and a four-fold range for epirubicin (38 to 120 mg m^{-2}). This is more in keeping with the known interpatient variation in drug clearance for these drugs. However, it would be better to achieve an individualised dose variation from the first dose rather than the third, fourth or fifth dose. To achieve this, the dose calculation method must take into account the activity of the elimination processes for the drug(s) in question before the first treatment is given.

FIXED DOSE?

Until better dose calculation methods are determined most clinicians will continue with the traditional method using BSA. However, clinicians

should be mindful of the inaccuracies of this system and should not be duped by its pseudo-scientific use of formulas and slide rules. Doses should be rounded liberally. Fractional doses are irrelevant and unnecessary. Furthermore they are expensive and possibly unsafe. It is unreasonable to use a small portion of an extra vial of chemotherapy if the dose prescribe is inaccurate 40% of the time. Ask your pharmacist whether he/she can really draw up 215 mg of DTIC (instead of 200 or 220 mg), 85 mg of docetaxel (instead of 80 or 90 mg) or 63 mg of methotrexate. What is the additional cost of prescribing 305 mg of paclitaxel instead of 300 mg?

Consideration should be given to using a range of ‘fixed doses’ for a particular drug that could be used as the starting dose and for dose adjustments. Remember that drug elimination varies by at least four-fold between individuals. Can a clinically significant different pharmacodynamic effect be expected between 650 and 700 mg of 5FU? This probably holds true even for carboplatin where doses are determined as a function of glomerular filtration rate. There is still a margin of error in these calculations so dose rounding is also tenable in this situation. The alternative of using a fixed dose for chemotherapy has recently been suggested for cisplatin and irinotecan after investigators found no relationship between BSA and clearance for both of these drugs (de Jongh *et al*, 2001; Mathijssen *et al*, 2002).

GUIDELINES

Guidelines for dose calculation are listed in Table 4 and an example in Table 5. These are not comprehensive and should be used in conjunction with clinical experience and good clinical practice. Some of them are subjective and based on opinion and derived

Table 4 Twelve rules for dose calculation of cytotoxic chemotherapy

1. **BSA-calculated dose is inaccurate.** Do not use this as the **sole** parameter for dose calculation.
2. Do not use **extremes of BSA** to calculate dose (e.g. <1.5 and >2.0). The use of ideal body weight has no scientific basis. However, the presence of cachexia or obesity both affect drug handling.
3. Use BSA as a means to learn the **typical absolute dose range** of drugs for a particular protocol (e.g. a typical doxorubicin dose is 80 to 120 mg, not 60 mg m^{-2}). The best dose is likely to be in that range and independent of BSA.
4. **Round the calculated dose liberally.** Do not order 'fractional' dose size. e.g. 102 mg of doxorubicin should be 100, 67 mg of methotrexate should be 65 or 70 mg. This has safety, compounding and financial implication.
5. Always take **parameters other than BSA** into consideration when calculating dose (see points 6–9).
6. **Know how the drug is eliminated.** If you do not know, don't order the drug. Adjust the dose based on the appropriate tests of **drug elimination** e.g. serum creatinine, GFR, bilirubin, transaminases, or other specific tests of drug elimination as they become available (genotype, phenotype).
7. Check for other medications that may inhibit or enhance cytotoxic drug elimination (see Table 6).
8. Check for other parameters that affect **drug disposition** e.g. serum albumin, presence of ascites, cachexia, obesity, performance status.
9. Check for other factors that affect **normal tissue sensitivity** that may require dose reduction e.g. prior chemotherapy and radiotherapy, performance status, cachexia.
10. **Know that this dose will be incorrect in up to 40% of the time.** Approximately 10% of patients will be overdosed and 30% of patients will be underdosed.
11. **Measure a biological endpoint** such as myelosuppression to check affect of the administered dose. Adjust the subsequent dose **UP** as well as down accordingly. A suggested minimal neutrophil count nadir for myelosuppressive drugs is 1.5×10^9 per litre. Adjust all drugs in a regimen that have similar elimination routes (e.g. doxorubicin, vinca alkaloids, podophyllotoxins, irinotecan, taxanes).
12. Always have your dose calculation **checked** by someone else e.g. pharmacist or nurse.

Table 5 Case example

A 45 year old woman with metastatic breast cancer to liver and bone presents for chemotherapy and you are asked to order the treatment. It has been decided that a combination of doxorubicin and cyclophosphamide will be used. Her height is 160 cm and weight 92 kg. Using the Dubois formula, her body surface area is 1.95 m^2 . The protocol dose is doxorubicin 60 mg m^{-2} and cyclophosphamide 600 mg m^{-2} . Her FBC is normal.

How will you calculate the dose of chemotherapy? Is there any further information you need?

1. Both drugs are eliminated by the liver. You want to know that the liver functions tests are not grossly abnormal
 2. You want to know whether she is taking any other medications that may interfere with drug elimination (see Table 6).
 3. You want to know whether she has previously received chemotherapy or extensive radiotherapy since this may affect the bone marrow response to treatment.
- This is the patient's first dose of chemotherapy and she had radiotherapy to the breast after lumpectomy 2 years ago. Her liver functions tests are only mildly abnormal. She is on no other medications.

Initial calculation according to the protocol gives a doxorubicin dose of 117 mg and cyclophosphamide 1170 mg. What dose will you give? What factors affect your decision?

1. This patient is probably obese given her height and weight. It is known that drug clearance of both drugs is reduced in obese patients.
 2. You know that BSA-dose calculation is inaccurate.
 3. You know that doxorubicin comes in 50 mg ampoules and cyclophosphamide comes in 200 mg ampoule.
 4. You know that giving fractional doses are difficult to compound accurately and can lead to unnecessary costs.
- You decide to give a dose of doxorubicin 100 mg and cyclophosphamide 1000 mg.

What about subsequent doses?

You monitor the toxicity of the patient using neutropenia as a surrogate pharmacodynamic marker. You dose-reduce according to standard practice in the case of excessive toxicity. However, you also check for the absence of toxicity since you do not want the patient to be underdosed.

The patient has minimal toxicity. A nadir FBC shows a neutrophil count of 2.5×10^9 per litre and platelets of 180×10^9 per litre (no significant drop from pre-treatment level). You increase the dose for cycle 2 by 15–20% with appropriate rounding of dose (doxorubicin 120 mg, cyclophosphamide 1200 mg). You plan to check the nadir blood count after cycle 2.

from clinical practice while others are based on best evidence as reviewed in Gurney (1996). The guidelines allow a framework in which to work, in an area currently fraught with uncertainty. As other methods of dose calculation become available, they can be tested against these guidelines and adopted into clinical practice if found to be superior.

As yet there are no useful *in vivo* measures of drug elimination that can be used for dose calculation. Efforts have been aimed at predicting alteration in drug elimination in those with grossly abnormal liver or renal function with limited success. Carboplatin can be fairly accurately dosed by measuring the GFR. Guidelines exist for dose adjustment of other cytotoxic drugs that are predominantly renally excreted (Kintzel and Dorr, 1995). However, most cytotoxic drugs are largely hepatically eliminated. Attempts at using elevation of serum transaminases and alkaline phosphatase as a guide to dose adjustment have largely failed except perhaps for docetaxel (Alexandre *et al*, 2000).

Potential drug interactions is an extensive problem and warrants a separate review. Drug elimination can be enhanced by activation of the steroid xenobiotic receptor (SXR) and other nuclear receptors (Synold *et al*, 2001; Kast *et al*, 2002). SXR has multiple ligands including rifampicin, dexamethasone, cyproterone acetate, spirinolactone, St John's wort and others. SXR activation leads to upregulation of transcription of many elimination pathways including CYP3A4/5, 2B6, 2C8, MDR1, MRP2 and glutathione-S-transferase. Inhibition of CYP enzymes and MDR1 and probably other efflux pumps can occur with drugs such as cyclosporin, HMGCoA reductase inhibitors, verapamil, omeprazole and cimetidine. However, few clinically significant interactions have been documented or examined for cytotoxic chemotherapy. Anti-convulsant induction of CYP3A4 (phenytoin, phenobarbitone, carbamazepine) has been shown to affect the pharmacodynamics of paclitaxel, irinotecan and teniposide and concomitant administration of anti-convulsants with chemother-

Table 6 Commonly used drugs that affect CYP3A4/MDR1 elimination routes**Drugs that inhibit CYP3A4/MDR1** (decrease drug elimination)

Macrolide antibiotics (erythromycin, clarithromycin)
 Azole antifungal agents (fluconazole, ketoconazole, itraconazole)
 Antidepressants (nefazodone, fluvoxamine)
 HIV protease inhibitors (amprenavir, indinavir, nelfinavir, zidovudine, zalcitabine, didanosine, zalcitabine, zalcitabine)
 HMG-CoA reductase inhibitors (lovastatin, simvastatin, atorvastatin)
 Cimetidine
 Verapamil
 Diltiazem
 Cisapride
 Cyclosporin

Drugs that induce CYP3A4/MDR1 (increase drug elimination)

Rifampicin
 Dexamethasone
 Cyproterone acetate
 Spirinolactone
 Phenytoin
 Carbamazepine
 Phenobarbitone
 St. John's wort (hyperforin)

Cytotoxic drugs that are eliminated by CYP3A4/MDR1

(competitive inhibition)

Anthracyclines
 Vinca alkaloids
 Taxanes
 Irinotecan
 Podophylotoxins
 Ifosfamide
 Cyclophosphamide

apy has been associated with a worse disease-free survival in children with acute lymphoblastic leukaemia (Chang *et al*, 1998;

Friedman *et al*, 1999; Relling *et al*, 2000). Table 6 lists commonly used drugs which may interfere with cytotoxic drug elimination, focusing on the CYP3A4/MDR1 axis since this is the major elimination route for most cytotoxic drugs and the site of most potential drug interactions.

THE FUTURE

Studies are underway to define the drug handling genotype and phenotype before drug administration so an individualised dose can be given on the first cycle (Gurney *et al*, 1998, 2001; Kuehl *et al*, 2001; Tanabe *et al*, 2001; Schott *et al*, 2001; Zhang *et al*, 2001). Assessment of both hepatic metabolism and active biliary excretion is essential since these are the important elimination processes for the majority of cytotoxic drugs. Such *in vivo* tests of drug handling would have the advantage of being applicable to a range of cytotoxic and non-cytotoxic drugs, cleared by similar mechanisms.

One scenario is that the majority of patients who have 'normal' drug elimination receive a standard fixed dose of drug according to the regimen. Pretreatment *in vivo* tests of genotype or phenotype will identify the estimated 20 to 30% of patients who fall into the extremes of drug elimination capability. These patients will receive significantly lower or higher fixed doses. In other words, starting doses will be a range of fixed doses according to low, normal or high drug elimination. Fine-tuning of doses will be based on the presence or absence of toxicity or some other parameter that measures biological effect.

BSA-dosing can no longer be viewed as an inaccuracy causing minor inconvenience in treatment of cancer patients. We have the means to solve this problem and it is important that we do so swiftly. Identification of drug handling capability before treatment can allow the abandonment of BSA-dosing and avoid serious but often unrecognised underdosing.

REFERENCES

- Alexandre J, Bleuzen P, Bonnetterre J, Sutherland W, Misset JL, Guastalla J, Viens P, Faivre S, Chahine A, Spielman M, Bensmaine A, Marty M, Mahjoubi M, Cvitkovic E (2000) Factors predicting for efficacy and safety of docetaxel in a compassionate-use cohort of 825 heavily pretreated advanced breast cancer patients. *J Clin Oncol* **18**: 562–573
- Berch J, Wiklund T, Erikstein B, Lidbrink E, Lindman H, Malmstrom P, Kellokumpu-Lehtinen P, Bengtsson NO, Soderlund G, Anker J, Wist E, Ottosson S, Salminen E, Ljungman P, Holte H, Nilsson J, Blomqvist C, Wilking N (2000) Tailored fluorouracil, epirubicin, and cyclophosphamide compared with marrow-supported high-dose chemotherapy as adjuvant treatment for high-risk breast cancer: a randomised trial. Scandinavian Breast Group 9401 study. *Lancet* **356**: 1384–1391
- Bishop JF, Dewar J, Toner GC, Smith J, Tattersall MH, Olver IN, Ackland S, Kennedy I, Goldstein D, Gurney H, Walpole E, Levi J, Stephenson J, Canetta R (1999) Initial paclitaxel improves outcome compared with CMFP combination chemotherapy as front line therapy in untreated metastatic breast cancer. *J Clin Oncol* **17**: 2355–2364
- Budman DR, Berry DA, Cirincione CT, Henderson IC, Wood WC, Weiss RB, Ferre CR, Muss HB, Green MR, Norton L, Frei III E (1998) Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. The Cancer and Leukemia Group B. *J Natl Cancer Inst* **90**: 1205–1211
- Carpenter JT, Maddox WA, Laws HL, Wirtschafter DD, Soong SJ (1982) Favorable factors in the adjuvant therapy of breast cancer. *Cancer* **50**: 18–23
- Chang SM, Kuhn JG, Rizzo J, Robins HI, Schold Jr SC, Spence AM, Berger MS, Mehta MP, Bozik ME, Pollack I, Gilbert M, Fulton D, Rankin C, Malec M, Prados MD (1998) Phase I study of paclitaxel in patients with recurrent malignant glioma: a North American Brain Tumor Consortium report. *J Clin Oncol* **16**: 2188–2194
- Cortes EP, Holland JF, Wang JJ, Sinks LF, Blom J, Senn H, Bank A, Glidewell O (1974) Amputation and adriamycin in primary osteosarcoma. *N Engl J Med* **291**: 998–1000
- de Jongh FE, Verweij L, Loos WJ, de Wit R, de Jonge MJ, Planting AS, Nooter K, Stoter G, Sparreboom A (2001) Body-Surface area-based dosing does not increase accuracy of predicting cisplatin exposure. *J Clin Oncol* **19**: 3733–3739
- Early Breast Cancer Trialists' Collaborative Group (1998) Polychemotherapy for early breast cancer: an overview of the randomised trials. *Lancet* **352**: 930–934
- Etienne MC, Lagrange JL, Dassonville O, Fleming R, Thyss A (1994) Population study of dihydropyrimidine dehydrogenase in cancer patients. *J Clin Oncol* **12**: 2248–2253
- Friedman HS, Petros WP, Friedman AH, Schaaf LJ, Kerby T, Lawyer J, Parry M, Houghton PJ, Lovell S, Rasheed K, Cloughsey T, Stewart ES, Colvin OM, Provenzale JM, McLendon RE, Bigner DD, Cokgor I, Haglund M, Rich J, Ashley D, Malczyn J, Elfring GL, Miller LL (1999) Irinotecan therapy in adults with recurrent or progressive malignant glioma. *J Clin Oncol* **17**: 1516–1525
- Gaemlin E, Boisdron-Celle M, Guerin-Meyer V, Delva R, Lortholary A, Genevieve F, Larra F, Ifrah N, Robert J (1999) Correlation between uracil and dihydrouracil plasma ratio, fluorouracil (5-FU) pharmacokinetic parameters, and tolerance in patients with advanced colorectal cancer: A potential interest for predicting 5-FU toxicity and determining optimal 5-FU dosage. *J Clin Oncol* **17**: 1105–1110
- George J, Byth K, Farrell GC (1996) Influence of clinicopathological variables on CYP protein. *J Gastroenterol Hepatol* **11**: 33–39
- Gurney H, Dodwell D, Thatcher N, Tattersall MHN (1993) Escalating drug delivery in cancer chemotherapy: A review of concepts and practice – part 1. *Annals Oncol* **4**: 23–34

- Gurney H (1996) Dose calculation of anticancer drugs: a review of the current practice and introduction of an alternative. *J Clin Oncol* **14**: 2590–2611
- Gurney HP, Ackland S, GebSKI V, Farrell G (1998) Factors affecting epirubicin pharmacokinetics and toxicity: evidence against using body-surface area for dose calculation. *J Clin Oncol* **16**: 2299–3004
- Gurney H, Ackland S, Liddle C, Dunleavy R, Rivory L, Farlow D, Evans S, Garg M, GebSKI V, Collins M, Farrell G (2001) Determining the drug elimination phenotype: Hepatic sestamibi scan and midazolam clearance as in vivo tests for drug metabolism and biliary elimination. *Proc Am Soc Clin Oncol* **20**: 305 (abstract)
- Horwich A, Sleijfer DT, Fossa SD, Kaye SB, Oliver RT, Cullen MH, Mead GM, de Wit R, de Mulder PH, Dearnaley DP, Cook PA, Sylvester RJ, Stenning SP (1997) Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer: a Multiinstitutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial. *J Clin Oncol* **15**: 1844–1852
- Hovgaard D, Nissen NI (1992) A phase I/II study of dose and administration of non-glycosylated bacterially synthesized G-M CSF in chemotherapy-induced neutropenia in patients with non-Hodgkin's lymphomas. *Leuk Lymphoma* **7**(3): 217–224
- International Germ Cell Consensus Classification (1997) A prognostic factor-based staging system for metastatic germ cell cancers. *J Clin Oncol* **15**: 594–603
- Kast HR, Goodwin B, Tarr PT, Jones SA, Anisfeld AM, Stoltz CM, Tontonoz P, Kliewer S, Willson TM, Edwards PA (2002) Regulation of multidrug resistance-associated protein 2 (MRP2/ABCC2) by the nuclear receptors PXR, FXR, and CAR. *J Biol Chem* **277**: 2908–2915
- Kintzel PE, Dorr RT (1995) Anticancer drug renal toxicity and elimination: dosing guidelines for altered renal function. *Cancer Treat Rev* **21**: 33–64
- Kuehl P, Zhang J, Lin Y, Lamba J, Assem M, Schuetz J, Watkins PB, Daly A, Wrighton SA, Hall SD, Maurel P, Relling M, Brimer C, Yasuda K, Venkataraman R, Strom S, Thummel K, Boguski MS, Schuetz E (2001) Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. *Nat Genet* **4**: 383–391
- Mathijssen RHJ, Verweij J, Maja JA, de Jonge MJA, Nooter K, Stoter G, Sparreboom A (2002) Impact of body-size measures on irinotecan clearance: Alternative dosing recommendations. *J Clin Oncol* **20**: 81–87
- McIntyre OR, Leone L, Pajak TF (1978) The use of intravenous melphalan (L-PAM) in the treatment of multiple myeloma. *Blood* **52**(Suppl 1): 274
- Poikonen P, Saarto T, Lundin J, Joensuu H, Blomqvist C (1999) Leucocyte nadir as a marker for chemotherapy efficacy in node-positive breast cancer treated with adjuvant CMF. *Br J Cancer* **80**(11): 1763–1766
- Rankin EM, Mill L, Kaye SB, Atkinson R, Cassidy L, Cordiner J, Cruickshank D, Davis J, Duncan ID, Fullerton W, Habeshaw T, Kennedy J, Kennedy R, Kitchener H, MacLean A, Paul J, Reed N, Sarker T, Soukop M, Swapp GH, Symonds RP (1992) A randomised study comparing standard dose carboplatin with chlorambucil and carboplatin in advanced ovarian cancer. *Br J Cancer* **65**: 275–281
- Ratain MJ, Mick R, Schilsky RL, Vogelzang NJ, Berezin F (1991) Pharmacologically based dosing of etoposide: a means of safely increasing dose intensity. *J Clin Oncol* **9**: 1480–1486
- Ratain MJ (1998) Body-surface area as a basis for dosing of anticancer agents: science, myth, or habit? *J Clin Oncol* **16**: 2297–2298
- Relling MV, Pui CH, Sandlund JT, Rivera GK, Hancock ML, Boyett JM, Schuetz EG, Evans WE (2000) Adverse effect of anticonvulsants on efficacy of chemotherapy for acute lymphoblastic leukaemia. *Lancet* **356**: 285–290
- Samson MK, Rivkin SE, Jones SE, Costanzi JJ, LoBuglio AF, Stephens RL, Gehan EA, Cummings GD (1984) Dose-response and dose-survival advantage for high versus low-dose cisplatin combined with vinblastine and bleomycin in disseminated testicular cancer. A Southwest Oncology Group study. *Cancer* **53**(5): 1029–1035
- Schott AF, Taylor LB, Baker L (2001) Individualized chemotherapy dosing based on metabolic phenotype. *Proc Am Soc Clin Oncol* **20**: 306 (abstract)
- Silber JH, Fridman M, DiPaola RS, Erder MH, Pauly MV, Fox KR (1998) First-cycle blood counts and subsequent neutropenia, dose reduction, or delay in early-stage breast cancer therapy. *J Clin Oncol* **16**(7): 2392–2400
- Stadtmauer EA, O'Neill A, Goldstein LJ, Crilley PA, Mangan KF, Ingle JN, Brodsky I, Martino S, Lazarus HM, Erban JK, Sickles C, Glick JH (2000) Conventional-dose chemotherapy compared with high-dose chemotherapy plus autologous hematopoietic stem-cell transplantation for metastatic breast cancer. Philadelphia Bone Marrow Transplant Group. *N Engl J Med* **342**: 1069–1076
- Synold TW, Dussault I, Forman BM (2001) The orphan nuclear receptor SXR coordinately regulates drug metabolism and efflux. *Nat Med* **7**: 584–590
- Tanabe M, Ieiri I, Nagata N, Inoue K, Ito S, Kanamori Y, Takahashi M, Kurata Y, Kigawa J, Higuchi S, Terakawa N, Otsubo K (2001) Expression of P-glycoprotein in human placenta: relation to genetic polymorphism of the multidrug resistance (MDR)-1 gene. *J Pharmacol Exp Ther* **297**: 1137–1143
- Wrighton SA, VandenBranden M, Ring BJ (1996) The human drug metabolizing cytochromes P450. *J Pharmacokinet Biopharm* **24**: 461–473
- Zhang J, Kuehl P, Green ED, Touchman JW, Watkins PB, Daly A, Hall SD, Maurel P, Relling M, Brimer C, Yasuda K, Wrighton SA, Hancock M, Kim RB, Strom S, Thummel K, Russell CG, Hudson Jr JR, Schuetz EG, Boguski MS (2001) The human pregnane X receptor: genomic structure and identification and functional characterization of natural allelic variants. *Pharmacogenetics* **7**: 555–572

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Appendix HOSEIN02

RESEARCH ARTICLE

Open Access

A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma

Peter J. Hosein^{1*}, Jessica Macintyre², Carolina Kawamura³, Jennifer Cudris Maldonado⁴, Vinicius Ernani⁵, Arturo Loaiza-Bonilla⁶, Govindarajan Narayanan⁷, Afonso Ribeiro⁸, Lorraine Portelance⁹, Jaime R. Merchan¹⁰, Joe U. Levi¹¹ and Caio M. Rocha-Lima¹²

Abstract

Background: 5-fluorouracil, leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) is superior to gemcitabine in patients with metastatic pancreatic cancer who have a good performance status. We investigated this combination as neoadjuvant therapy for locally advanced pancreatic cancer (LAPC).

Methods: In this retrospective series, we included patients with unresectable LAPC who received neoadjuvant FOLFIRINOX with growth factor support. The primary analysis endpoint was R0 resection rate.

Results: Eighteen treatment-naïve patients with unresectable or borderline resectable LAPC were treated with neoadjuvant FOLFIRINOX. The median age was 57.5 years and all had ECOG PS of 0 or 1. Eleven (61 %) had tumors in the head of the pancreas and 9 (50 %) had biliary stents placed prior to chemotherapy. A total of 146 cycles were administered with a median of 8 cycles (range 3-17) per patient. At maximum response or tolerability, 7 (39 %) were converted to resectability by radiological criteria; 5 had R0 resections, 1 had an R1 resection, and 1 had unresectable disease. Among the 11 patients who remained unresectable after FOLFIRINOX, 3 went on to have R0 resections after combined chemoradiotherapy, giving an overall R0 resection rate of 44 % (95 % CI 22–69 %). After a median follow-up of 13.4 months, the 1-year progression-free survival was 83 % (95 % CI 59-96 %) and the 1-year overall survival was 100 % (95 % CI 85-100 %). Grade 3/4 chemotherapy-related toxicities were neutropenia (22 %), neutropenic fever (17 %), thrombocytopenia (11 %), fatigue (11 %), and diarrhea (11 %). Common grade 1/2 toxicities were neutropenia (33 %), anemia (72 %), thrombocytopenia (44 %), fatigue (78 %), nausea (50 %), diarrhea (33 %) and neuropathy (33 %).

Conclusions: FOLFIRINOX followed by chemoradiotherapy is feasible as neoadjuvant therapy in patients with unresectable LAPC. The R0 resection rate of 44 % in this population is promising. Further studies are warranted.

Keywords: Pancreatic ductal carcinoma, neoadjuvant therapy, surgery, radiation therapy

Background

Pancreatic cancer carries a dismal prognosis with a 5-year overall survival rate of 6 %. It is the fourth leading cause of cancer death in the USA with an estimated 37,660 deaths in 2011 [1]. Surgery remains the best chance for cure but only 10-20 % of patients will be candidates for curative resection at diagnosis. Up to 40 % of

newly diagnosed patients will present with locally advanced, unresectable disease because of vascular encasement, and consensus criteria now exist to clearly define this group [2]. Up to one-third of patients who initially have locally advanced, unresectable disease may become resectable after neoadjuvant therapy [3]. These patients can have comparable survival to those who were initially resectable.

Systemic chemotherapy for advanced pancreatic cancer has generally been disappointing. The traditional gemcitabine-based therapies result in low response rates

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and short survival times in the range of 6 months. Interest in systemic chemotherapy for this disease was recently rejuvenated with the advent of the FOLFIRINOX combination (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) [4]. In the randomized phase III ACCORD-11 trial, FOLFIRINOX was shown to be superior to single-agent gemcitabine in response rate (RR), progression-free survival (PFS) and overall survival (OS). The RR in the FOLFIRINOX arm was 32 % versus 9 % in the gemcitabine arm, and this translated into an improvement in PFS to 6.4 months (versus 3.3 in the control arm, $p < 0.0001$) and OS of 11.1 months (versus 6.8 months in the control arm, $p < 0.0001$). This trial only enrolled patients with metastatic pancreatic cancer. In the setting of LAPC, a good tumor response is a desirable goal since tumor shrinkage away from vascular structures may lead to resectability.

Radiation therapy may be beneficial in patients with LAPC and combined chemoradiotherapy (CCRT) has been tested in this population. Although 5-FU-based CCRT is commonly used in this setting, gemcitabine-based CCRT is safe and effective [5,6]. The best sequence of treatment administration has not been established. Prospective randomized trials are ongoing to evaluate whether there is a survival benefit of CCRT versus chemotherapy alone. Retrospective data suggest superiority of sequencing chemotherapy followed by chemoradiation [7]. The theoretical advantages of this approach include eradicating micrometastatic disease early on, and also identifying patients who progress early and develop metastases during initial chemotherapy (an estimated 25-30 % of patients), thus avoiding morbidities associated with radiotherapy in this group of patients.

Our group at the University of Miami adopted the approach of induction chemotherapy followed by CCRT in patients with unresectable or borderline resectable LAPC. Although the phase III results supporting the use of FOLFIRINOX in pancreatic cancer were only recently presented in 2010, the initial FOLFIRINOX randomized phase II trial (reported in 2007) showed a similarly high RR [8]. After these promising results were presented, we began using this regimen in patients with borderline resectable (BR) or unresectable (UR) LAPC. The aim of this retrospective study was to define the efficacy and toxicities of this regimen in LAPC, especially in patients with pancreatic head tumors and biliary obstruction – a group that was relatively underrepresented in the ACCORD-11 trial.

Patients and Methods

We performed a retrospective analysis at the University of Miami Sylvester Comprehensive Cancer Center and Jackson Memorial Hospital in Miami, Florida of all patients with LAPC who received first-line treatment

with FOLFIRINOX. Patients were identified by searching the pancreatic cancer database which was approved by the University of Miami Institutional Review Board (IRB). This IRB-approved database provided a waiver of the requirement for informed consent for retrospective studies and allowed for publication of de-identified data.

The medical, radiation and surgical oncologists in the group developed an algorithm for uniform treatment of this group of patients as follows. Patients were selected for treatment with FOLFIRINOX if they had a histological or cytological diagnosis of pancreatic adenocarcinoma, an Eastern Cooperative Group performance status (ECOG PS) of 0 or 1, adequate organ function, and UR/BR LAPC. For patients who presented with biliary obstruction, adequate biliary drainage was required prior to initiation of this chemotherapy. The determination of resectability was made by multidisciplinary review. Since there is currently no internationally agreed-upon definition of borderline-resectable LAPC, we applied the American Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract (AHPBA/SSO/SSAT) criteria [2]. These criteria are summarized in Table 1. The data used to determine resectability included pretreatment contrast-enhanced CT scans (CECT's) and endoscopic ultrasound (EUS) in all patients and surgical exploration when available.

Table 1 Criteria used for determining resectability for non-metastatic pancreatic cancer

Category	Criteria [§]
Resectable	<ul style="list-style-type: none"> • No evidence of SMV and portal vein abutment, distortion, tumor thrombus or venous encasement • Clear fat planes around the celiac axis, hepatic artery and SMA
Borderline resectable	<ul style="list-style-type: none"> • Venous involvement of the SMV/portal vein demonstrating tumor abutment with or without impingement and narrowing of the lumen, encasement of the SMV/portal vein but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumor thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction. • Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis • Tumor abutment of the SMA not to exceed 180 degrees of the circumference of the vessel wall
Unresectable	<ul style="list-style-type: none"> • Major venous thrombosis of the portal vein or SMV extending for several centimeters • Circumferential encasement of the SMA, celiac axis or proximal hepatic artery

Abbreviations: SMA: Superior mesenteric artery; SMV: Superior mesenteric vein.

[§]Adapted from the American Hepato-Pancreato-Biliary Association/ Society of Surgical Oncology/ Society for Surgery of the Alimentary Tract (AHPBA/SSO/SSAT) criteria (reference 2).

Treatment with FOLFIRINOX proceeded with doses identical to the ACCORD-11 trial [4]. On day 1 of every 14-day cycle, oxaliplatin was administered at a dose of 85 mg per square meter, irinotecan at 180 mg per square meter, folinic acid at 400 mg per square meter, and 5-fluoruracil (5-FU) as a bolus of 400 mg per square meter. 5-FU was then administered as a continuous infusion of 2400 mg per square meter over 46 hours. Filgrastim was at the discretion of the treating physician. Treatment continued until progression of disease, intolerable toxicity or maximum response. Toxicities were assessed at every fortnightly visit and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4 [9]. Criteria for dose modification were similar to those described in the ACCORD-11 trial. Response assessment by CECT's were performed every 8 weeks on therapy or sooner if progression was suspected by symptoms or rising CA19-9.

After every CECT scan during treatment, each patient's case was reviewed at a multidisciplinary conference to determine whether the reason for defining the patient as UR or BR had improved. Since size was not the only criteria used in this evaluation, traditional response criteria (such as RECIST) were not employed. For example, if a tumor was categorized as BR due to abutment of the SMA up to 180°, the extent of abutment was re-evaluated after every scan to determine if this was improving and if the patient would now be a surgical candidate. If two consecutive scans during treatment showed similar findings with no improvement, this was considered to be the maximum response. Maximum tolerability was defined as the point when excessive toxicities warranted stopping FOLFIRINOX, even if a patient had not achieved their maximum response. Because we used an algorithm of real-time monitoring of response and toxicity, there was no predefined minimum or maximum number of cycles.

At maximum response or tolerability, patients who appeared to be resectable by imaging criteria were offered surgical exploration and resection (within 6-8 weeks after chemotherapy) followed by postoperative CCRT. Patients who remained unresectable at maximum response or tolerability of FOLFIRINOX were offered CCRT. For radiation sensitization, patients received concurrent gemcitabine at 600 mg per square meter per week. Intensity-modulated radiation therapy (IMRT) was delivered in a standard fashion to a total dose of 50.4 Gy in 28 fractions. At the end of CCRT, patients were re-evaluated with CECT's to determine resectability. Post-CCRT treatment was left to the discretion of the treating physicians.

The primary endpoint for this analysis was the R0 resection rate. An R0 resection was defined as at least 1 mm free margins. An R1 resection was defined as tumor within 1 mm from the closest margin. Secondary

endpoints included safety, tolerability, overall survival and progression-free survival. All patients who received at least one cycle of FOLFIRINOX were included in the analysis. PFS and OS were calculated as follows; PFS was defined as the duration in months from the date of the first cycle of FOLFIRINOX until the date of documented progression, recurrence or death, whichever was sooner. OS was defined as the duration in months from the date of the first cycle of FOLFIRINOX until the date of death from any cause. Patients known to be alive were censored at the time of last contact. PFS and OS were estimated by the Kaplan–Meier method with corresponding two-sided 95 % CI's for survival proportions based on Greenwood's

Table 2 Patient characteristics, n = 18

n (%)	
Age	
Median	57.5 years
Range	41 – 73 years
Sex	
Male	10 (56 %)
Female	8 (44 %)
ECOG Performance status	
0	8 (44 %)
1	10 (56 %)
Pancreatic tumor location	
Head	11 (61 %)
Uncinate process	3 (17 %)
Body	2 (11 %)
Tail	2 (11 %)
Biliary stent	
Yes	9 (50 %)
No	9 (50 %)
Serum bilirubin level prior to chemotherapy	
Median	0.35 mg/dl
Range	0.1 – 1.2 mg/dl
Basis for unresectability	
Borderline resectable	
SMV encased (short segment)	3 (17 %)
SV encased	1 (6 %)
Unresectable	
SMV encased (long segment)	1 (6 %)
SMA encased	3 (17 %)
HA encased	2 (11 %)
Celiac trunk encased	3 (17 %)
Confluence of PV, SV and SMV encased	5 (28 %)

Abbreviations: HA: Hepatic artery; PV: Portal vein; SMA: Superior mesenteric artery; SMV: Superior mesenteric vein; SV: Splenic vein.

variance and the log-transform method [10]. Descriptive statistics were also used to summarize data.

Results

Between 5/2008 and 5/2011 we administered FOLFIRINOX to 18 treatment-naïve patients with UR/BR LAPC. The baseline characteristics of these patients are summarized in Table 2. One patient was defined as unresectable at the time of exploratory laparotomy and the remaining patients fulfilled criteria for UR/BR disease based on CECT and EUS findings. One patient who had splenic vein encasement was potentially resectable according to the AHPBA/SSO/SSAT criteria but underwent neoadjuvant therapy because the tumor was large and ill defined and the multidisciplinary group felt that the patient would benefit from neoadjuvant therapy. Among the 11 patients who had tumors at the head of the pancreas, 9 had metallic stents placed to relieve biliary obstruction and the other 2 had double-bypass operations which included a choledochojejunostomy. All patients who had stents or bypass procedures achieved normalization of their serum bilirubin levels prior to the start of chemotherapy.

Figure 1 shows the patient flow through the treatment algorithm. After FOLFIRINOX therapy, 7 patients had disease that was radiologically assessed as being potentially resectable. Five of these went on to have R0 resections, one R1 and one was grossly unresectable at exploration. Among the remaining 11 patients, one developed progression after 3 cycles and 10 went on to receive CCRT. Among these 10 patients, 2 were ongoing on CCRT at the time of this report; 5 remained with unresectable disease; and 3 were radiologically assessed as being potentially resectable after CCRT and all 3 went on to have R0 resections. The overall R0 resection rate was 8 out of 18 or 44 % (95 % CI 22-69 %) using this sequential combined modality approach. Among the 8 patients with successful R0 resections, the median number of FOLFIRINOX cycles delivered was 6 (range 5-17). In these patients, the reasons for UR/BR at baseline were SMV encasement in 2 patients, SMV/portal vein confluence encasement (2 patients), SMA encasement >180 degrees (1 patient), hepatic artery encasement (2 patients) and splenic vein encasement (1 patient).

With a median follow-up of 13.4 months, 2 patients have died and 2 others are alive with progression of

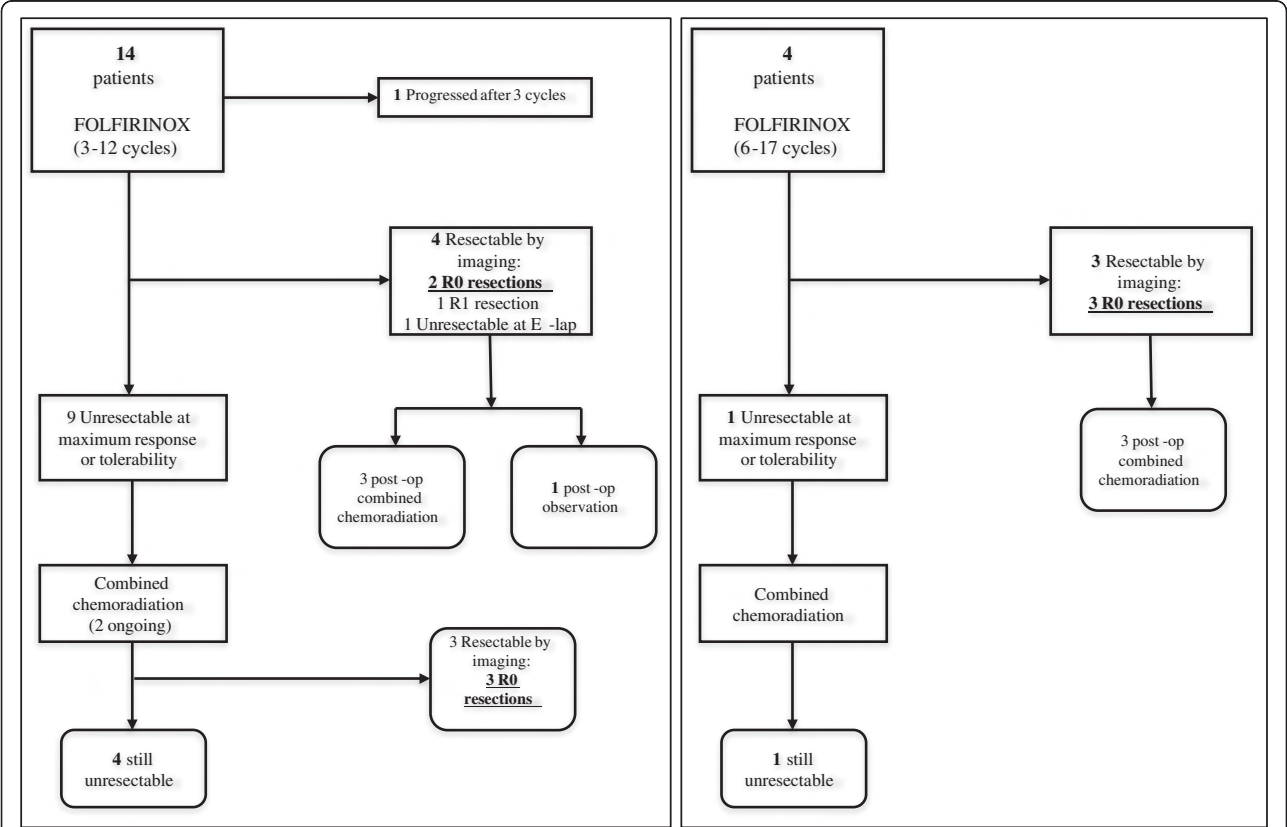


Figure 1 Patient flowchart for patients assessed as having unresectable disease (panel 1A, n = 14), and for those assessed as having borderline resectable disease (panel 1B).

disease. One of the patients who died had an R0 resection and progressed 11 months after surgery. The Kaplan-Meier estimated median PFS and OS have not been reached. The 1-year PFS was 83 % (95 % CI 59-96 %) and the 1-year OS was 100 % (95 % CI 85-100 %). The estimated 1-year PFS was not significantly different for the patients who achieved R0 resections (88 %; 95 % CI 47-100 %) versus those who did not (80 %; 95 % CI 44-94 %, $p=0.27$). Figure 2 shows the Kaplan-Meier plots for PFS and OS, including a stratification by resection status.

A total of 146 cycles of FOLFIRINOX were delivered among the 18 patients treated, with a median of 8 cycles per patient. Twenty-five cycles (17 %) were given at a reduced dose, with 7 of these (5 %) being given without irinotecan in one patient. Table 3 summarizes the treatment delivery. All patients experienced at least one

grade 1 or 2 adverse event and 8 patients (44 %) experienced at least one grade 3 or 4 adverse event. The adverse event profile is shown in Table 4. There were no significant differences in the toxicity profile for patients who had biliary stents versus those who did not. Filgrastim was used in 89 % of patients, and was started prophylactically from cycle 1 in 50 %; in spite of this, 22 % of patients had grade 3 or 4 neutropenia and 17 % had neutropenic fever. No patient had to be taken off FOLFIRINOX for toxicity. Ten patients (56 %) had a treatment delay of at least one week due to toxicity (most commonly for neutropenia or neutropenic fever). There were no episodes of cholangitis during FOLFIRINOX in any of the 18 patients treated.

Among the 10 patients who went to surgery after FOLFIRINOX, 3 experienced significant postoperative

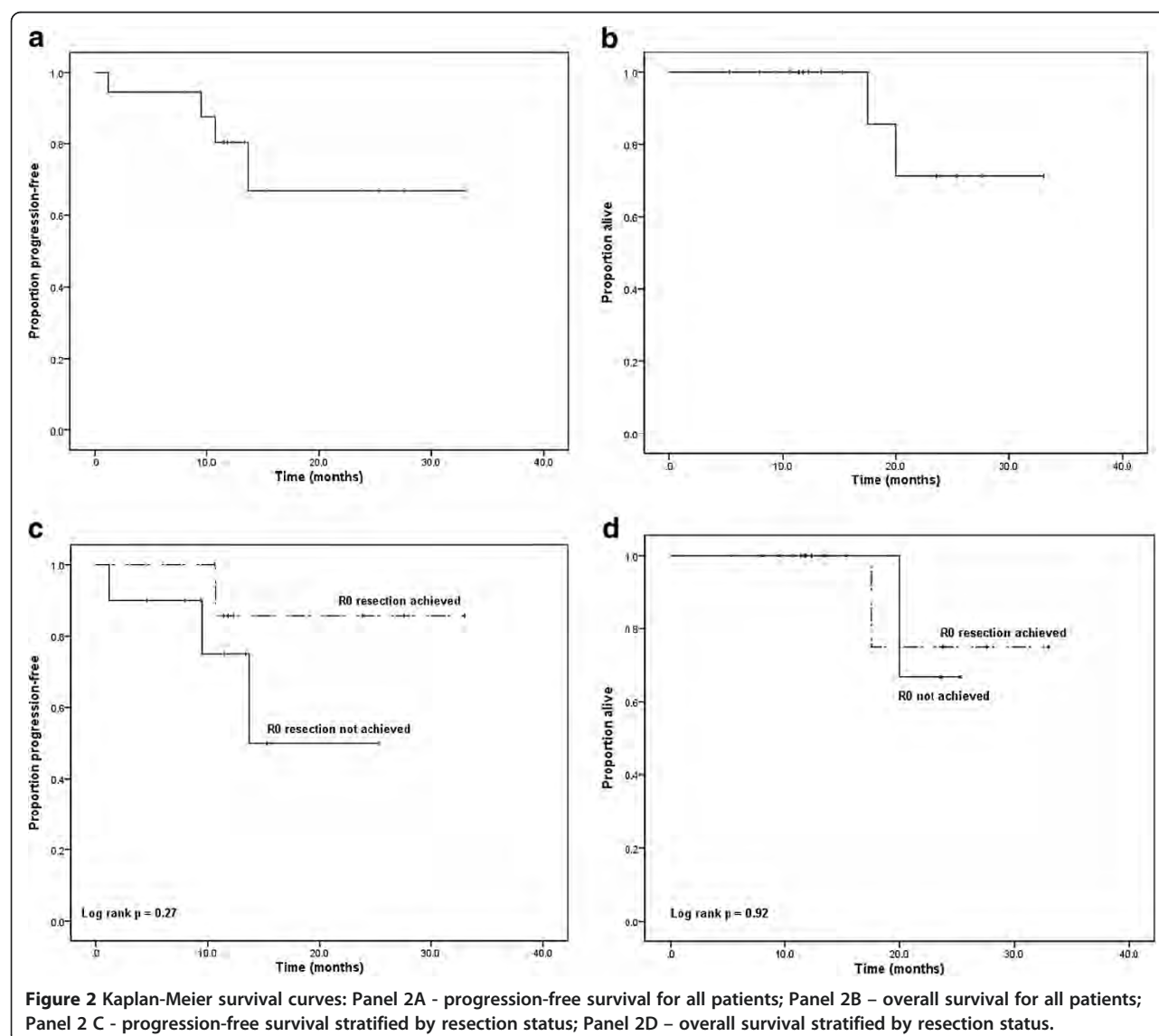


Table 3 Treatment delivery, n = 18

	n (%)
Number of cycles	
≤ 4	2 (11 %)
5-8	8 (44 %)
9-12	7 (39 %)
≥ 13	1 (6 %)
Median	8 cycles
Dose intensity*	
Total number of cycles	146
Number of cycles at full dose	121 (83 %)
Number of cycles at reduced dose	25 (17 %)
Number of cycles delayed by ≥ 1 week	13 (9 %)
5-Fluorouracil dose intensity	98 %
Irinotecan dose intensity	95 %
Oxaliplatin dose intensity	98 %

*Dose intensity is defined as the dose delivered divided by the full dose.

complications. One patient developed *C. Difficile* colitis, gastroparesis and a subhepatic collection; one had an infected pancreatic bed collection requiring percutaneous drainage 3 times; and one had an infected splenic bed collection requiring percutaneous drainage. None of these patients received preoperative radiation. The median length of perioperative hospital stay for these 10 patients was 7 days (range 5 to 60).

Discussion

FOLFIRINOX can be considered a new standard of care option in patients with metastatic pancreatic cancer with

a good performance status. In a survey of the prescribing plans of American oncologists after the 2010 American Society of Clinical Oncology meeting (during which the ACCORD-11 phase III results were presented), 18 % planned to offer FOLFIRINOX to good performance status patients, compared with 0 % in the same survey in 2009 [11]. However, FOLFIRINOX has not been readily adopted by the oncology community in the US because of concerns for the tolerability of this regimen and the risk of cholangitis in patients with stents [12,13]. Some of these concerns were quieted with the publication of the full report of the ACCORD-11 trial, in which no cholangitis was observed and the rate of febrile neutropenia was only 5.4 % [4].

The current study represents the first published series of North American patients treated with FOLFIRINOX with locally advanced pancreas cancer. The regimen's toxicity was for the most part reversible and manageable. We selected relatively young patients with excellent performance status and little or no comorbidities. We believe that patient selection for FOLFIRINOX cannot be overemphasized since we have anecdotally observed significantly poorer tolerability in older patients and those with major comorbidities. Furthermore, we believe that our practice of limiting the use of FOLFIRINOX to patients who had adequate biliary drainage also helped to lessen the toxicities since irinotecan depends on biliary elimination. Despite the use of prophylactic filgrastim in most patients, 3 (17 %) developed febrile neutropenia, including 2 who had biliary stents in place. The other common toxicities such as fatigue, nausea and diarrhea were manageable, and no patient had to be

Table 4 Adverse events during chemotherapy (18 patients, 146 cycles)

Adverse event	Patients with biliary stent (n = 9)		Patients without biliary stent (n = 9)		All patients (n = 18)	
	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 1/2 n (%)	Grade 3/4 n (%)
Hematological						
Neutropenia	3 (33 %)	3 (33 %)	3 (33 %)	1 (11 %)	6 (33 %)	4 (22 %)
Neutropenic fever	0	2 (22 %)	0	1 (11 %)	0	3 (17 %)
Anemia	6 (67 %)	2 (22 %)	7 (78 %)	0	13 (72 %)	2 (11 %)
Thrombocytopenia	3 (33 %)	3 (33 %)	5 (56 %)	0	8 (44 %)	3 (17 %)
Non-hematological						
Fatigue	6 (67 %)	1 (11 %)	8 (89 %)	1 (11 %)	14 (78 %)	2 (11 %)
Anorexia	3 (33 %)	0	1 (11 %)	0	4 (22 %)	0
Mucositis	1 (11 %)	0	1 (11 %)	0	2 (11 %)	0
Nausea	5 (56 %)	0	4 (44 %)	0	9 (50 %)	0
Vomiting	0	0	2 (22 %)	0	2 (11 %)	0
Diarrhea	3 (33 %)	1 (11 %)	3 (33 %)	1 (11 %)	6 (33 %)	2 (11 %)
Peripheral neuropathy	1 (11 %)	0	5 (56 %)	0	6 (33 %)	0
Alopecia	6 (67 %)	0	6 (67 %)	0	12 (67 %)	0

taken off chemotherapy due to intolerance. Although the full dose of the regimen could be delivered in 85 % of the administered cycles, treatment delays for toxicity were common. In an attempt to attenuate the toxicities of this regimen, the US cooperative groups are planning FOLFIRINOX studies without the 5-FU bolus and with mandatory prophylactic growth-factor support.

Our strategy of neoadjuvant FOLFIRINOX followed by CCRT in patients with UR/BR LAPC resulted in an R0 resection rate of 44 %, with 2 patients in the denominator still receiving CCRT. Although the follow-up is relatively short, only 2 patients have died and 7 of the 8 patients who underwent R0 resections remain progression-free at a median follow-up of 14.9 months. For patients who remained unresectable after FOLFIRINOX, CCRT was able to convert 3 out of 10 (30 %) to resectability, and may have provided some measure of disease control to the others whose disease remained unresectable. Interestingly, a recently reported study of gemcitabine-based CCRT (using the identical CCRT regimen used in our series) reported resections in only 2 out of 28 (7 %) patients [5]. Since our series is small and the event rate is low, it is difficult to draw definite conclusions. Nonetheless, we hypothesize that the use of induction treatment with FOLFIRINOX, followed by a non-cross resistant chemotherapeutic agent as a radiation sensitizer (gemcitabine) might be an advantageous strategy to improve response rates and resectability.

Conclusions

Neoadjuvant therapy with FOLFIRINOX in patients with unresectable or borderline resectable locally advanced pancreatic cancer appears to be feasible in selected patients. Continued follow-up will determine if achieving an R0 resection will translate into a survival advantage in this group of patients. Further study of this sequential combined modality approach is warranted.

Competing interests

The authors declare that they have no competing interest.

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Authors' contributions

PJH, JM and CRL conceived the study, collected, analyzed and interpreted the data and drafted the manuscript. CK, JCM, ALB, GN, AR, LP, JRM and JUL made substantial contributions to data collection and analysis and drafting the manuscript. All authors approved the final version of the manuscript.

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References

1. American Cancer Society: *Cancer Facts & Figures 2011*. Atlanta: American Cancer Society; 2011.
2. Callery MP, Chang KJ, Fishman EK, Talamonti MS, William Traverso L, Linehan DC: **Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement.** *Ann Surg Oncol* 2009, **16**(7):1727–33.
3. Gillen S, Schuster T, Meyer Zum Büschenfelde C, Friess H, Kleeff J: **Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages.** *PLoS Med* 2010, **7**(4):e1000267.
4. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bannoun J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M: **Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer.** *N Engl J Med* 2011, **364**(19):1817–25.
5. Cardenes HR, Moore AM, Johnson CS, Yu M, Helft P, Chiorean EG, Vinson J, Howard TJ, Stephens AW, Tai DF, Loehrer PJ Sr: **A Phase II Study of Gemcitabine in Combination With Radiation Therapy in Patients With Localized, Unresectable, Pancreatic Cancer: A Hoosier Oncology Group Study.** *Am J Clin Oncol* 2011, **34**(5):460–5.
6. Loehrer PJ Sr, Feng Y, Cardenes H, Wagner L, Brell JM, Cella D, Flynn P, Ramanathan RK, Crane CH, Alberts SR, Benson AB 3rd: **Gemcitabine Alone Versus Gemcitabine Plus Radiotherapy in Patients With Locally Advanced Pancreatic Cancer: An Eastern Cooperative Oncology Group Trial.** *J Clin Oncol* 2011, **29**(31):4105–4112.
7. Huguet F, André T, Hammel P, Artru P, Balosso J, Selle F, Deniaud-Alexandre E, Ruszniewski P, Touboul E, Labianca R, de Gramont A, Louvet C: **Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies.** *J Clin Oncol* 2007, **25**(3):326–31.
8. Ychou M, Desseigne F, Guimbaud R, Ducreux M, Bouché O, Bécouarn Y, Adenis A, Montoto-Grillot C, Luporsi E, Conroy T: **Randomized phase II trial comparing FOLFIRINOX vs gemcitabine as first-line treatment for metastatic pancreatic adenocarcinoma. First results of the ACCORD 11 trial.** *J Clin Oncol* 2007, **25**(suppl 18):4516.
9. National Cancer Institute: *Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.*; 2009.
10. Collett D: *Modelling survival data in medical research*. London: Chapman & Hall; 1994.
11. Bendell JC, Britton S, Green MR, et al: **Immediate impact of the FOLFIRINOX phase III data reported at the 2010 ASCO Annual Meeting on prescribing plans of American oncology physicians for patients with metastatic pancreas cancer (MPC).** *J Clin Oncol* 2011, **29**(Suppl 4):286.
12. Kang SP, Saif MW: **Three-drug combination regimen in pancreatic cancer treatment: are we there yet?** *JOP* 2011, **12**:78–82.
13. Kim R: **FOLFIRINOX: a new standard treatment for advanced pancreatic cancer?** *Lancet Oncol* 2010, **12**:8–9.

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Appendix JAMES01

Meeting Abstract: 2014 ASCO Annual Meeting I

FREE ACCESS Gastrointestinal (Noncolorectal) Cancer May 20, 2014



Interim analysis of a phase II study of dose-modified FOLFIRINOX (mFOLFIRINOX) in locally advanced (LAPC) and metastatic pancreatic cancer (MPC).

Authors: [Edward Samuel James](#), [Xiaopan Yao](#), [Xiangyu Cong](#), [Jia Li](#), [Carol Hahn](#), [Kristin Kaley](#), [Jeremy S. Kortmansky](#), ... [SHOW ALL](#) ... , and [Jill Lacy](#) | [AUTHORS INFO & AFFILIATIONS](#)

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Abstract

e15226

Background: Although FOLFIRINOX is superior to gemcitabine in MPC, the regimen is associated with significant toxicities (Conroy et al. N Engl J Med 2011;364:1817). In our prior retrospective analysis, efficacy was not compromised by dose attenuations of FOLFIRINOX (Gunturu et al. Med Oncol 2013;30:361). Based on this analysis, we are conducting a prospective, phase II, open-label study to evaluate the efficacy and tolerability of mFOLFIRINOX in pts with advanced pancreatic cancer (PC). **Methods:** Previously untreated pts with MPC or LAPC received mFOLFIRINOX with 25% dose reductions of irinotecan and bolus 5-FU given every two wks until progression, unacceptable toxicity, or surgical resection. All pts received prophylactic pegfilgrastim. FDG-PET scans were obtained at baseline and after 2 cycles. CAT scans were obtained after every 4 cycles. Toxicities and response rate (RR) were compared to historical data reported by Conroy.

Results: 62 pts with ECOG PS ≤ 1 have been enrolled between 11/2011 and 12/2013, Pt characteristics: LAPC 27; MPC 35; median age 62 yrs (range 46-86); male 37. Median number of cycles was 8 (range 1-21). Grade 3/4 toxicities were: vomiting, peripheral sensory neuropathy (PSN) - 3.2%; ALT elevated, thromboembolism, febrile neutropenia - 4.8%; anemia - 6.4%; diarrhea, neutropenia - 16.2%; fatigue - 12.9%; thrombocytopenia - 11.3%. Neutropenia ($p < 0.0001$) and vomiting ($p = 0.006$) were significantly decreased. There was a nonsignificant trend toward a lower incidence of fatigue ($p = 0.05$). Response by RECIST (CR+PR) in 29 evaluable pts with MPC was 31.4% (0 CR, 11 PR, 15 SD, 3 PD) and similar to historical data (31.6%; $p = 0.82$). 9/21 evaluable pts with LAPC underwent resection (43%). 16/43 pts evaluable for PET response had a $> 50\%$ decrease in SUV(max)(37%). **Conclusions:** Findings from our interim analysis suggests that mFOLFIRINOX, given along with prophylactic pegfilgrastim is associated with a similar RR and improved tolerability compared to full dose FOLFIRINOX in advanced PC. In pts with LAPC, neoadjuvant

FOLFIRINOX appears to have substantial activity with 43% of evaluable pts undergoing resection. Planned accrual has been completed. Interim OS and PFS will be reported. [Clinical trial information: NCT01523457.](#)

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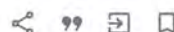
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Appendix JIAO02

Comparative effectiveness of NALIRIFOX vs. FOLFIRINOX in pancreatic cancer.

Xiayu Jiao, Afsaneh Barzi; University of Southern California, Los Angeles, Los Angeles, CA; Medical Oncology and Therapeutics, City of Hope/AccessHope, Duarte, CA

Background: Metastatic pancreatic cancer is associated with limited survival, poor quality of life, and limited treatment options. FOLFIRINOX and gemcitabine/nab-paclitaxel (GNP) are associated with survival gain compared to gemcitabine and NALIRIFOX is associated with survival improvement compared to GNP. NALIRIFOX and FOLFIRINOX are not directly compared to each other. We conducted an analysis of oncologic benefits and costs of NALIRIFOX vs. FOLFIRINOX. **Methods:** A cost-effectiveness model was developed using partitioned survival analysis with three health states: progression-free, progression, and death. Data on overall survival and progression-free survival were derived from PRODIGE and NAPOLI-3 published data to reconstruct the states in the model. The time horizon of the model was set to 36 months. Costs included treatment costs and adverse event management as well as supportive care cost. We used Veteran Affairs' data for unit cost of each agent. To calculate the cost of treatment we assumed the average body surface area to be 1.79. Five adverse events (AEs) were included in the cost analysis: neutropenia, febrile neutropenia, anemia, diarrhea, and thrombocytopenia. We used the utility of 0.80 during PFS and 0.73 during progression for assessment of Quality Adjusted Life Year (QALY). The benefits and costs of treatment was calculated and used to estimate the incremental cost-effectiveness ratio (ICER) of NALIRIFOX compared with FOLFIRINOX. **Results:** The calculated PFS for FOLFIRINOX was 6.8 months and for NALIRIFOX was 8.9 months. Compared to FOLFIRINOX, NALIRIFOX was associated with an improvement in life year gain (11.97 months vs. 10.95 months). The monthly acquisition cost for NALIRIFOX was \$13,610 and for FOLFIRINOX \$5,501. Based on the probabilities of selected AEs, the monthly cost of AE management for NALIRIFOX was \$5,589 and for FOLFIRINOX was \$15,511. QALY for NALIRIFOX was 10.23 and for FOLFIRINOX was 9.59 months. The incremental cost effectiveness ratio for NALIRIFOX vs. FOLFIRINOX was \$1,368,937. **Conclusions:** In this modeling analysis, NALIRIFOX is associated with improvement in PFS and QALY. The analysis highlights the importance of AE management for improving quality of life and cost in the recipients of FOLFIRINOX. The economic value for use of NALIRIFOX is very high and outside of any conventional boundary of acceptable value threshold for treatment. Research Sponsor: None.

Appendix KAGA01

Early tumor shrinkage as a predictor of favorable outcomes in patients with advanced pancreatic cancer treated with FOLFIRINOX

Yasuhiro Kaga^{1,*}, Yu Sunakawa^{1,*}, Yutaro Kubota², Teppei Tagawa², Taikan Yamamoto¹, Toshikazu Ikusue¹, Yu Uto¹, Kouichirou Miyashita¹, Hirokazu Toshima³, Kouji Kobayashi³, Atsushi Hisamatsu³, Wataru Ichikawa⁴, Takashi Sekikawa⁴, Ken Shimada³, Yasutsuna Sasaki²

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ABSTRACT

There are several reports on the correlation between early tumor shrinkage (ETS) or depth of response (DpR) and survival in chemotherapies for colorectal cancer; however, few studies have investigated it in pancreatic cancer. We therefore investigated whether the ETS will predict outcomes in 59 patients with advanced pancreatic cancer treated with FOLFIRINOX therapy. The association of ETS with progression-free survival (PFS) and overall survival (OS) was evaluated but also we addressed to the correlation between outcomes and DpR. ETS was defined as a reduction $\geq 20\%$ of target lesions' diameters measured at 6 to 8 weeks from treatment start. DpR was percentage of maximal tumor shrinkage observed at the nadir diameter compared with baseline. Among 47 evaluable patients for the ETS, 12 (25.5%) patients experienced ETS. The ETS was significantly associated with better PFS (9.0 vs. 4.2 months) as well as OS (24.0 vs. 9.1 months); moreover, the association had a statistically significance for PFS but a strong trend for OS in multivariate analysis. The DpR was statistically significantly but weakly associated with OS. In conclusion, this is the first report that the early response to chemotherapy may predict favorable outcomes in patients with advanced pancreatic cancer treated with FOLFIRINOX therapy.

INTRODUCTION

Pancreatic cancer is the fourth leading cause of death from cancer over the world, which is usually a high grade of malignancy at the diagnosis and is one of intractable cancers [1]. It carries a severe prognosis, which 5-year survival rate was reported to be lower than 5% [1]. In addition, the morbidity of the disease is increasing in recent year; therefore, more than 30,000 people die of pancreatic cancer every year in Japan [2]. Advanced pancreatic cancer remains an incurable disease with few cure treatments. The phase III PRODIGE 4/ACCORD 11 trial

provided one of current standard regimens for advanced pancreatic cancer, consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX), which has superior response rate (RR) and survival benefit even with severe toxicity in patients with advanced pancreatic cancer. The RR, median progression-free survival (PFS), and overall survival (OS) were significantly better in patients receiving FOLFIRINOX therapy compared to patients receiving gemcitabine therapy (RR, 31.6% vs. 9.4%; median PFS, 6.4 months vs. 3.3 months, HR 0.47, 95% CI 0.37–0.59, $P < 0.001$; median OS, 11.1 months vs. 6.8 months, HR 0.57, 95% CI 0.45–0.73, $P < 0.001$)

[3]. Since then, FOLFIRINOX regimen has been used as a standard first-line treatment for patients with advanced pancreatic cancer; however, there are still no biomarkers to predict favorable outcomes of the FOLFIRINOX. There have been several reports on the correlation between early tumor shrinkage (ETS) or depth of response (DpR) and survival time in chemotherapies for metastatic colorectal cancer [4–7]. The phase III TRIBE trial compared first-line FOLFOXIRI plus bevacizumab with FOLFIRI plus bevacizumab for unresectable metastatic colorectal cancer patients. In a subgroup analysis of the TRIBE trial, a highly significant correlation of both ETS and DpR with survival parameters (PFS, post progression survival, and OS) was reported in the arm of triplet plus bevacizumab treatment [5]. Moreover, a subgroup analysis of the phase III FIRE-3 trial which evaluated first-line FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab also demonstrated a strong correlation of ETS with PFS and OS [8]. Recently, Heinemann V et al. reviewed the ETS and DpR for colorectal cancer treatment and evaluated their potential as predictive markers for the clinical management. The review showed that the ETS not only relates to a prognostic category but also distinguishes patients with high sensitivity to treatment and more favorable prognosis from a heterogeneous group of patients classified as no ETS [4]. An observational cohort study for advanced pancreatic cancer patients treated with the triplet regimen has revealed Eastern Cooperative Oncology Group (ECOG) performance status (PS), liver metastases, and neutrophil-to-lymphocyte ratio as the most important predictors of survival [9]. However, to the best of our knowledge, there have been few studies to investigate the association between ETS or DpR and clinical outcomes of chemotherapy in pancreatic cancer. We therefore investigated whether the ETS will predict outcomes in patients with advanced pancreatic cancer treated with FOLFIRINOX therapy.

RESULTS

Patient characteristics

Between November 2012 and November 2015, 59 patients were enrolled from 3 institutions of Showa University (Showa University Northern Yokohama Hospital, Showa University Hospital, and Showa University Koto Toyosu Hospital). The patient characteristics at baseline are shown in Table 1. The median age was 63 years (range, 34–76), forty-four patients (74.6%) had a PS of 0. The primary site of tumor was the head of pancreas in 26 patients (44.1%). Thirteen patients (22.0%) had a biliary stent, and 47 patients (79.7%) had metastatic diseases. Forty patients (67.8%) were treated with FOLFIRINOX as a first-line treatment. In the all population, RR, median PFS, and OS were 27.3%, 5.3 months (95% CI, 4.2–7.9), and 10.3 months (95% CI, 7.6–11.1), respectively.

Association between response to the treatment and clinical outcomes

Among all enrolled patients, 4 patients were not evaluable for response due to patients with locally advanced diseases or peritoneal diseases. Among 55 evaluable patients for response, 15 (27.3%) patients achieved a partial response. The OS was statistically significantly longer in responders compared to non-responders (24.0 months vs. 9.0 months, HR 0.33, 95% CI 0.12–0.75, log-rank $P = 0.010$). No significant association was observed between response and PFS (Table 2).

Forty-seven (79.6%) of all 59 patients had measurable tumors for the ETS. Among the evaluable patients for the ETS, 12 (25.5%) patients experienced an ETS. The PFS was statistically significantly longer in patients with ETS compared to those with no ETS (9.0 months vs. 4.2 months, HR 0.43, 95% CI 0.18–0.91, log-rank $P = 0.032$). Moreover, patients with ETS had a significantly better OS (24.0 months vs 9.1 months, HR 0.36, 95% CI 0.12–0.87, log-rank $P = 0.031$) (Table 2, Figure 1).

Association between DpR and clinical outcomes

Thirty-one patients (52.5%) who experienced an OS event were estimated for the DpR. Median DpR was –10.3% (from –75.7 to 100). The DpR was statistically significantly but weakly associated with OS ($r_s = 0.18$, $P = 0.017$) and was not associated with PFS (Figure 2).

Multivariate analysis

We performed a multivariate analysis for several variables including response and ETS to precisely evaluate the association with clinical outcomes. In the multivariate analysis adjusted for ECOG PS and diagnosis, the response was statistically significantly associated with both PFS and OS (HR 0.38; 95% CI 0.18–0.80; $P = 0.011$, HR 0.33; 95% CI 0.13–0.79; $P = 0.013$, respectively). On the contrary, the ETS had a significant association with PFS ($P = 0.02$) but a strong trend with OS ($P = 0.065$) (Table 3).

DISCUSSION

We analyzed the associations between ETS or DpR and clinical outcomes of FOLFIRINOX treatment in patients with advanced pancreatic cancer. To the best of our knowledge, the present analysis is the first attempt to evaluate the association of response to the intensive chemotherapy with survival parameters in pancreatic cancer. Our data showed that response had a significant correlation with OS in the assessable population. Moreover, the ETS was significantly associated with both PFS and OS, suggesting that achieving rapid and deeper response may lead not only to delay of disease progression but also to prolonged survival.

Table 1: Demographic and baseline characteristics of patients (n = 59)

Characteristics	
Age-year	
Median	63
Range	34–76
Sex-no.(%)	
Male	40 (67.8)
Female	19 (32.2)
ECOG PS-no.(%)	
0	44 (74.6)
1	15 (25.4)
Diagnosis-no (%)	
Locally advanced	12 (20.3)
Metastatic	47 (79.7)
Synchronous	38
Metachronous	9
Treatment line-no (%)	
First-line	40 (67.8)
Second-line	19 (32.2)
Pancreatic tumor location-no.(%)	
Head	26 (44.1)
Body	22 (37.3)
Tail	9 (15.3)
Multicentric	2 (3.4)
Biliary Stent-no.(%)	
Yes	13 (22.0)
No	46 (78.0)

Table 2: Associations of ETS and response with clinical outcomes

	ETS+ (n = 12)	ETS- (n = 35)	HR (95% CI)	P-value
PFS	9.0 months	4.2 months	0.43 (0.18-0.91)	0.032
OS	24.0 months	9.1 months	0.36 (0.12–0.87)	0.031
	Responder (n = 15)	Non-responder (n = 40)	HR (95% CI)	P-value
PFS	5.7 months	4.2 months	0.56 (0.27–1.07)	0.090
OS	24.0 months	9.0 months	0.33 (0.12–0.75)	0.010

ETS, early tumor shrinkage; PFS, progression-free survival; OS, overall survival.

FOLFIRINOX is now considered to be one of first-line standard treatments for patients with advanced pancreatic cancer according to results of the phase III trial by Conroy et al. [3]. However, it cannot be applied to all patients with pancreatic cancer due to severe toxicity of the FOLFIRINOX, such as neutropenia, leucopenia, febrile neutropenia, anorexia, and diarrhea. The study by Metges et al. who are the original investigators in the

PRODIGE 4/ACCORD 11 trial, based on their established criteria, showed that 81% of 242 patients required a dose reduction (median dose intensity; 5-FU bolus 82%, oxaliplatin 78%, irinotecan 81%), but that this result did not affect treatment efficacy compared to the PRODIGE 4/ACCORD 11 trial: RR 39% vs. 32%, median PFS 6.5 vs. 6.4 months, and median OS 10.9 vs. 11.1 months [10]. A Japanese phase II trial of the FOLFIRINOX showed

that grade 3 or 4 neutropenia and febrile neutropenia were more frequently observed compared to those in the global phase III trial (77.8% vs. 45.7%, 22.2% vs. 5.4%, respectively) [11]. Recently, several clinical studies of a modified FOLFIRINOX regimen have been carried out to reduce its toxicities. Blazer et al. reported their experience with reducing irinotecan in addition to dropping 5-FU bolus, and also concluded that the modified regimen was effective and well tolerated with no episodes of grade 3 or 4 neutropenia and thrombocytopenia, but with 46% of patients requiring a dose reduction for other toxicities [12]. Another Japanese phase II trial which evaluated the efficacy and safety of modified FOLFIRINOX regimen with intravenous oxaliplatin 85 mg/m², irinotecan

150 mg/m², 5-FU infusion 2400 mg/m² over 46 hours, and no bolus 5-FU, demonstrated that the modified regimen has an improved safety profile with maintained efficacy in advanced pancreatic cancer [13]. We therefore clinically utilized irinotecan dosage of 150 mg/m² for patients enrolled in this study. The survival time (median PFS, 5.3 months; median OS, 10.3 months) in our cohort was similar to that of the Japanese phase II trial of FOLFIRINOX (median PFS, 5.6 months; median OS 10.7 months) as well as the FOLFIRINOX phase III trial (median PFS, 6.4 months; median OS, 11.1 months) [11].

In addition to considering more proper dosage, it would be important to investigate novel predictors for efficacy and survival outcomes of the FOLFIRINOX

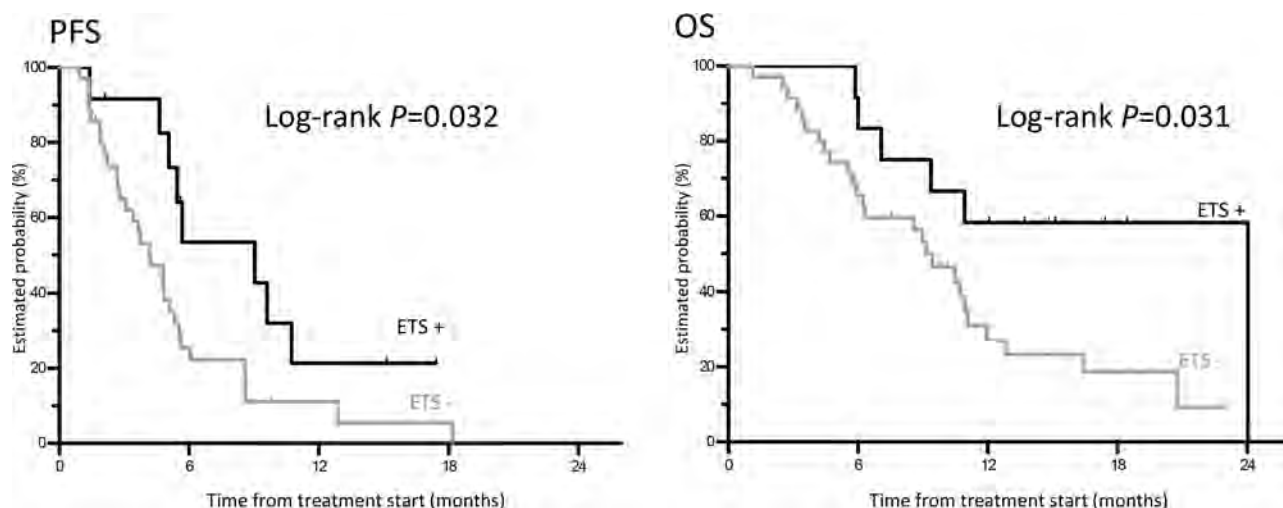


Figure 1: Kaplan-Meier curves for progression-free survival and overall survival in relation to early tumor shrinkage.

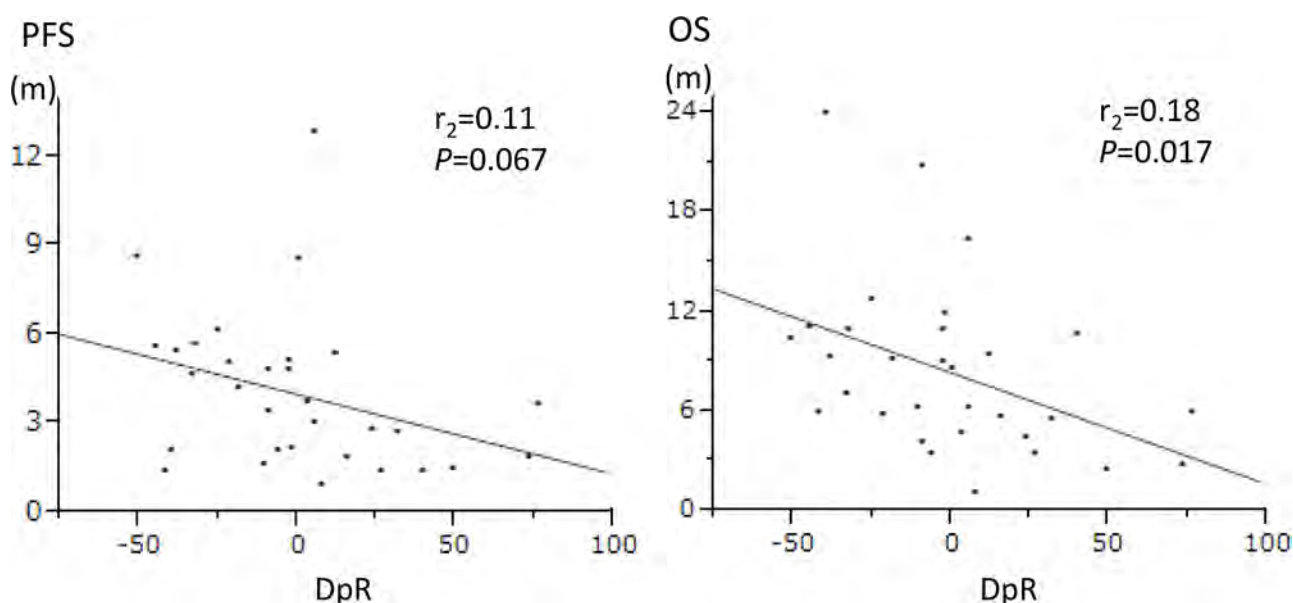


Figure 2: The correlation of depth of response (DpR) with clinical outcomes by the Spearman's rank correlation coefficient.

Table 3: Multivariate analysis

Variables	Progression-free survival			Overall survival		
	HR	95% CI	P-value*	HR	95% CI	P-value*
Gender						
Male vs. Female	1.06	0.56–2.00	0.87	0.93	0.48–1.81	0.82
ECOG PS						
0 vs. 1	0.56	0.29–1.09	0.086	0.45	0.22–0.91	0.026
Diagnosis						
Locally advanced vs. metastatic	0.32	0.12–0.84	0.021	0.33	0.11–0.94	0.037
Response						
Responder vs. non-responder	0.38	0.18–0.80	0.011	0.33	0.13–0.79	0.013
ETS						
ETS+ vs. ETS–	0.37	0.16–0.85	0.020	0.40	0.15–1.06	0.065

*P values were based on Wald test for PFS and OS in the multivariable Cox regression model adjusted for ECOG performance status (0 vs. 1) and diagnosis (locally advanced vs. metastatic).

treatment in pancreatic cancer. The predictive factor would enable physicians to distinguish patients who benefit more from the intensive chemotherapy with potentially severe toxicities. A subgroup analysis of the TRIBE trial evaluating a triplet regimen plus bevacizumab for colorectal cancer has reported ETS and DpR as promising surrogates for survival time [5]. The ETS, which is decrease in tumor load measured at the time of first imaging after the start of treatment, is considered to be an early indicator of sensitivity to chemotherapy for metastatic colorectal cancer. The DpR is defined as the percentage of tumor shrinkage, based on the longest diameters or reconstructed volume, observed at the lowest point, so called nadir, compared with baseline [4]. FOLFOXIRI plus bevacizumab improved the ETS and DpR when compared with FOLFIRI plus bevacizumab in a sub-analysis of the TRIBE trial [14]. Moreover, the analysis showed achieving rapid and deep tumor shrinkage consistently delayed tumor progression and prolonged survival in patients treated with the triplet-based regimen. Therefore, the ETS and DpR may become novel factors to predict favorable outcomes of FOLFIRINOX treatment in patients with advanced pancreatic cancer.

Our study could demonstrate for the first time that ETS to the intensive chemotherapy with triplet regimen may predict favorable outcomes in patients with advanced pancreatic cancer. The ETS was significantly associated with better PFS as well as OS in patients treated with the FOLFIRINOX therapy; moreover, the association had a statistically significance for PFS but a strong trend for OS in multivariate analysis. The responders had significantly longer OS compared to the non-responders in both univariate and multivariate analyses. In addition, the DpR was statistically significantly but weakly associated with OS but not PFS. The ETS is an assessment method that is usually judged at earlier timing from treatment start than response to chemotherapy and DpR; therefore, it

may enable us to distinguish patients earlier, who benefit more from FOLFIRINOX therapy. Survival time is much shorter in pancreatic cancer compared to colorectal cancer, leading to shorter treatment duration. Thus, it may be reasonable to switch regimen for ETS-negative patients. Our findings and hypothesis need a prospective validation which may contain an adaptive trial design to evaluate treatment decision according to ETS status.

Our study was retrospective, and included a limited assessable population because of small number of patients. FOLFIRINOX regimen is usually used as a first-line treatment for advanced pancreatic cancer; therefore, the ETS and DpR should be investigated in patients receiving the triplet regimen as an initial therapy. We performed a sub-analysis according to treatment line; however, we failed to indicate the significant association between the biomarkers and clinical outcomes due to small sample size ($n = 31$) (data not shown). It is desirable to assess them prospectively for achieving more accurate results using larger patient cohorts. In previously reported trials which investigated association of the ETS with clinical outcomes, the tumor assessment was carried out every 8 weeks until the evidence of disease progression by means of computer tomography scan [4, 5, 15]; however, we measured target lesions for assessment of ETS at 6 or 8 weeks from treatment start due to retrospective trial and limited data, causing a difference in the timing of evaluation for ETS from previous reports. We therefore should integrate the term of evaluation for ETS in future studies.

In conclusion, the ETS and DpR were significantly associated with clinical outcomes in advanced pancreatic cancer patients treated with FOLFIRINOX chemotherapy. Our results also suggest that the early response to the triplet regimen may predict better clinical outcomes in patients with advanced pancreatic cancer. These findings are warranted to validate in future trials.

MATERIALS AND METHODS

Patient

This study enrolled advanced pancreatic cancer patients with an ECOG PS of 0 or 1, and adequate hematological, liver, and renal function, who received FOLFIRINOX as first- or second-line treatment between November 2012 and November 2015 in 3 institutions of Showa University (Showa University Northern Yokohama Hospital, Showa University Hospital, and Showa University Koto Toyosu Hospital). All clinical data were obtained retrospectively from their medical records.

Treatment

We utilized the FOLFIRINOX with modified dosage according to the Japanese phase II trial [13]: irinotecan was also infused intravenous (i.v.) over 90 minutes at 150 mg/m² and then 2 hours i.v. infusion of oxaliplatin at 85 mg/m² and 2 hours i.v. infusion of l-leucovorin at 200 mg/m² followed by continuous i.v. infusion of 5-FU over 46 hours at 2400 mg/m². This regimen was repeated every two weeks until disease progression. Dose modifications were made at the treating physician's discretion. Patient received palonosetron, aprepitant, and dexamethasone for emesis prophylaxis.

Study design

We retrospectively analyzed characteristics, RR, PFS, and OS in patients enrolled in this study. The objectives of our study were to evaluate the association of ETS with PFS and OS but also to address the correlation between clinical outcomes and DpR. Responses were evaluated according to the RECIST version 1.1 by the investigators. ETS was defined as a reduction $\geq 20\%$ of target lesions' diameters measured at 6 to 8 weeks from treatment start. DpR was defined as the percentage of maximal tumor shrinkage observed at the nadir diameter compared with baseline. A DpR of negative 100% indicates the complete disappearance of all target tumor lesions. We thought it was difficult to take an accurate measurement of the primary site of tumor in patients with locally advanced pancreatic cancer. Then, we mainly evaluated metastatic measurable lesions in patients with metastatic pancreatic cancer for evaluation of ETS and DpR.

Statistical analysis

Kaplan-Meier analysis was used to generate survival curves of PFS and OS. The median survival time was compared using the log-rank test. The Spearman's rank correlation coefficient was adopted to evaluate the association between DpR and survival including PFS and

OS. Multivariate analysis was performed based on Wald test for PFS and OS in the multivariable Cox regression model adjusted for ECOG PS (0 vs. 1) and diagnosis (locally advanced vs. metastatic).

Statistical analyses were carried out using JMP 9.0.3 (SAS institute, Cary, NC, USA).

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CONFLICTS OF INTEREST

The authors disclose no potential conflicts of interest.

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REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012; 62:10–29. doi: 10.3322/caac.20138.
2. Center for Cancer Control and Information Services NCC, Japan. <http://www.ncc.go.jp/en/cis/index.html>.
3. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardiere C, Bennouna J, Bachet JB, Khemissa-Akouz F, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011; 364:1817–1825. doi: 10.1056/NEJMoa1011923.
4. Heinemann V, Stintzing S, Modest DP, Giessen-Jung C, Michl M, Mansmann UR. Early tumour shrinkage (ETS) and depth of response (DpR) in the treatment of patients with metastatic colorectal cancer (mCRC). *Eur J Cancer*. 2015. doi: 10.1016/j.ejca.2015.06.116.
5. Cremolini C, Loupakis F, Antoniotti C, Lonardi S, Masi G, Salvatore L, Cortesi E, Tomasello G, Spadi R, Zaniboni A, Tonini G, Barone C, Vitello S, et al. Early tumor shrinkage and depth of response predict long-term outcome in metastatic colorectal cancer patients treated with first-line chemotherapy plus bevacizumab: results from phase III TRIBE trial by the Gruppo Oncologico del Nord Ovest. *Ann Oncol*. 2015. doi: 10.1093/annonc/mdv112.
6. Piessevaux H, Buyse M, Schlichting M, Van Cutsem E, Bokemeyer C, Heeger S, Tejpar S. Use of early tumor shrinkage to predict long-term outcome in metastatic colorectal cancer treated with cetuximab. *J Clin Oncol*. 2013; 31:3764–3775. doi: 10.1200/JCO.2012.42.8532.
7. Douillard JY, Siena S, Peeters M, Koukakis R, Terwey JH, Tabernero J. Impact of early tumour shrinkage and resection on outcomes in patients with wild-type RAS metastatic

colorectal cancer. *Eur J Cancer*. 2015; 51:1231–1242. doi: 10.1016/j.ejca.2015.03.026.

8. Stintzing S, Modest DP, Fischer von Weikersthal L, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran S, Heintges T, Lerchenmueller C, Kahl C, Seipelt G, Kullmann F, Scheithauer W, et al. LBA11 Independent Radiological Evaluation of Objective Response Early Tumor Shrinkage, and Depth Of Response In FIRE-3 (AIO KRK-0306) in the Final RAS Evaluable Population. *Annals of Oncology*. 2014; 25. doi: 10.1093/annonc/mdl438.9.
9. Vivaldi C, Caparello C, Musettini G, Pasquini G, Catanese S, Fornaro L, Lencioni M, Falcone A, Vasile E. First-line treatment with FOLFOXIRI for advanced pancreatic cancer in clinical practice: Patients' outcome and analysis of prognostic factors. *Int J Cancer*. 2016; 139:938–945. doi: 10.1002/ijc.30125.
10. Metges JP, Ramee JF, Douillard J-Y, Boucher E, Faroux R, Guerin-Meyer V, Cumin I, Miglianico L, Le Roux C, Dupuis O, Pomeuf M, Lam YH, Achour N, et al. Efficacy and safety of FOLFIRINOX in patients with metastatic pancreatic cancer. *ASCO Meeting Abstracts*. 2014; 32:305.
11. Okusaka T, Ikeda M, Fukutomi A, Ioka T, Furuse J, Ohkawa S, Isayama H, Boku N. Phase II study of FOLFIRINOX for chemotherapy-naïve Japanese patients with metastatic pancreatic cancer. *Cancer Sci*. 2014; 105:1321–1326. doi: 10.1111/cas.12501.
12. Blazer MA, Wu CS-Y, Goldberg RM, Phillips GS, Schmidt CR, Muscarella P, El-Dika SS, Walker JP, Krishna SG, Groce JR, Wuthrick EJ, Williams TM, Efries D, et al. Tolerability and efficacy of modified FOLFIRINOX (mFOLFIRINOX) in patients with borderline-resectable pancreatic cancer (BRPC) and locally advanced unresectable pancreatic cancer (LAURPC). *ASCO Meeting Abstracts*. 2014; 32:275.
13. Ueno M, Ozaka M, Ishii H, Sato T, Ikeda M, Uesugi K, Sata N, Miyashita K, Mizuno N, Tsuji K, Okusaka T, Furuse J. Phase II study of modified FOLFIRINOX for chemotherapy-naïve patients with metastatic pancreatic cancer. *ASCO Meeting Abstracts*. 2016; 34:4111.
14. Cremolini C, Loupakis F, Antoniotti C, Lonardi S, Masi G, Salvatore L, Cortesi E, Tomasello G, Spadi R, Zaniboni A, Tonini G, Barone C, Vitello S, et al. Early tumor shrinkage and depth of response predict long-term outcome in metastatic colorectal cancer patients treated with first-line chemotherapy plus bevacizumab: results from phase III TRIBE trial by the Gruppo Oncologico del Nord Ovest. *Ann Oncol*. 2015; 26:1188–1194. doi: 10.1093/annonc/mdv112.
15. Tsuji A, Sunakawa Y, Ichikawa W, Nakamura M, Kochi M, Denda T, Yamaguchi T, Shimada K, Takagane A, Tani S, Kotaka M, Kuramochi H, Furushima K, et al. Early Tumor Shrinkage and Depth of Response as Predictors of Favorable Treatment Outcomes in Patients with Metastatic Colorectal Cancer Treated with FOLFOX Plus Cetuximab (JACCRO CC-05). *Target Oncol*. 2016. doi: 10.1007/s11523-016-0445-6.

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Appendix KANG02

Retrospective Study

Comparison of efficacy and safety between standard-dose and modified-dose FOLFIRINOX as a first-line treatment of pancreatic cancer

Huapyeong Kang, Jung Hyun Jo, Hee Seung Lee, Moon Jae Chung, Seungmin Bang, Seung Woo Park, Si Young Song, Jeong Youp Park

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Author contributions: Kang H and Park JY led the study design; the study was supervised by Park JY. Kang H, Jo JH, Lee HS, Chung MJ, Bang S, Park SW, Song SY, and Park JY were contributed to the collection and assembly of data; Kang H did the data analysis; all authors interpreted the analyzed data; Kang H and Park JY wrote the manuscript; all authors reviewed every version of the manuscript and approved the final manuscript.

Institutional review board statement: This study was approved by the Institutional Review Board of Yonsei University Health System (Approval number: 4-2017-0757) and carried out in accordance with the Declaration of Helsinki.

Informed consent statement: The institutional review board waived the need for consent for this study due to its retrospective design.

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Data sharing statement: No additional data are available.

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Abstract

AIM

To directly compare the efficacy and toxicity of standard-dose FOLFIRINOX (sFOLFIRINOX) and modified-dose FOLFIRINOX (mFOLFIRINOX, 75% of standard-dose) for pancreatic cancer.

METHODS

One hundred and thirty pancreatic cancer patients who received sFOLFIRINOX ($n = 88$) or mFOLFIRINOX ($n = 42$) as their first-line chemotherapy from January 2013 to July 2017 were retrospectively reviewed. For efficacy analysis, the objective response rate (ORR),

disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) were evaluated and compared using Pearson's chi-square test, Kaplan-Meier plot and log-rank test. The adverse events (AEs) were evaluated, and severe ($\geq$ grade 3) AEs rates of the two groups were compared for toxicity analysis.

RESULTS

The mFOLFIRINOX group included more female patients (30.7% *vs* 57.1%; $P = 0.004$) and older patients [age (median), 57 *vs* 63.5; $P = 0.018$] than the sFOLFIRINOX group. In the efficacy analysis, the ORR and DCR were not significantly different between the two groups (ORR: 39.8% *vs* 35.7%; $P = 0.656$; DCR: 80.7% *vs* 83.3%; $P = 0.716$). The median PFS and OS were also not different between the groups (PFS: 8.7 mo *vs* 8.1 mo, $P = 0.272$; OS: 13.9 mo *vs* 13.7 mo, $P = 0.476$). In the safety analysis with severe AEs, the rates of neutropenia (83.0% *vs* 66.7%; $P = 0.044$), anorexia (48.9% *vs* 28.6%; $P = 0.029$) and diarrhea (13.6% *vs* 0.0%; $P = 0.009$) were markedly lower in the mFOLFIRINOX group.

CONCLUSION

mFOLFIRINOX showed comparable efficacy but better safety compared to sFOLFIRINOX. If clinically necessary, initiating FOLFIRINOX with 75% of the standard-dose can alleviate toxicity concerns without compromising efficacy.

Key words: Dose modification; Adverse event; Pancreatic cancer; Adenocarcinoma; FOLFIRINOX; Chemotherapy

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Core tip: Although the efficacy of FOLFIRINOX for pancreatic cancer has been well demonstrated, its relatively high toxicity rate is an important concern. We aimed to directly compare the efficacy and toxicity of standard-dose FOLFIRINOX and modified-dose FOLFIRINOX (mFOLFIRINOX, 75% of standard-dose) for pancreatic cancer. One hundred and thirty patients with pancreatic cancer (standard: 88 *vs* modified: 42) were reviewed retrospectively. Response rates, progression-free survival, and overall survival were not different between both groups. However, severe adverse events such as neutropenia, anorexia and diarrhea were significantly lower in the mFOLFIRINOX group. If clinically necessary, initiating FOLFIRINOX with 75% of the standard-dose can alleviate toxicity concerns without compromising efficacy.

Kang H, Jo JH, Lee HS, Chung MJ, Bang S, Park SW, Song SY, Park JY. Comparison of efficacy and safety between standard-dose and modified-dose FOLFIRINOX as a first-line treatment of pancreatic cancer. *World J Gastrointest Oncol* 2018; 10(11): 421-430 Available from: URL: <http://www.wjgnet.com/1948-5204/full/v10/i11/421.htm> DOI: <http://dx.doi.org/10.4251/wjgo.v10.i11.421>

INTRODUCTION

Pancreatic cancer (PC) is the fourth-most common cause of cancer deaths estimated in the United States^[1]. It is also reported as the fifth-most common cause of cancer-related deaths in South Korea^[2]. Despite the introduction of several novel regimens, the five-year survival rate for all stages of PC remains around ten percent^[1,2]. These statistics are based on the fact that < 20% of newly diagnosed PC cases are suitable candidates for surgical resection, while disseminated disease was noted in > 50% of new cases^[1].

Ever since the survival benefit of gemcitabine in patients with advanced PC was reported, gemcitabine-based regimens have been primarily used for > twenty years^[3-6]. Recently, a non-gemcitabine-based combination regimen comprising folinic acid (FA), 5-fluorouracil (5-FU), irinotecan, and oxaliplatin (FOLFIRINOX) was introduced for metastatic PC (MPC). In the PRODIGE4/ACCORD11 randomized phase III trial, FOLFIRINOX was associated with a significant survival benefit compared to gemcitabine monotherapy as the first-line therapy for patients with MPC^[7]. Thereafter, several studies were conducted to determine the role of FOLFIRINOX in locally advanced PC (LAPC) or borderline resectable PC (BRPC), and meta-analysis reports showed promising improvements in median survivals and resection rates^[8,9]. Consequently, FOLFIRINOX is recommended as a preferred front-line therapy for MPC in major up-to-date guidelines and on the list of options for BRPC or LAPC, although prospective randomized data are still lacking^[10-12].

However, the relatively high toxicity of FOLFIRINOX is still a concern. In the PRODIGE4/ACCORD11 trial, FOLFIRINOX showed higher severe toxicity rates than gemcitabine, particularly for grade three or four neutropenia in 45.7% of patients^[7]. The National Comprehensive Cancer Network guidelines for PC restrict FOLFIRINOX to patients with Eastern Cooperative Oncology Group performance status (ECOG-PS) 0 or 1^[12]. Owing to the high toxicity profile of FOLFIRINOX, several retrospective studies and phase II trials using modified-dose FOLFIRINOX (mFOLFIRINOX) were performed with variable modification strategies. This research showed improved safety profiles and comparable efficacy^[13-17]. Nevertheless, clinical feasibility or optimal strategy for dose-modification of FOLFIRINOX still remains unclear, since previous studies on mFOLFIRINOX indirectly compared their results to those of the PRODIGE4/ACCORD11 trial. Direct comparative study between standard-dose FOLFIRINOX (sFOLFIRINOX) and mFOLFIRINOX is still lacking. Therefore, in this study, we directly compared the therapeutic efficacy and safety of sFOLFIRINOX and mFOLFIRINOX as first-line

chemotherapies for PC.

MATERIALS AND METHODS

Patient selection

All patients diagnosed with PC who received FOLFIRINOX as their first-line chemotherapy in Severance Hospital from January 2013 to July 2017 were retrospectively reviewed. The inclusion criteria were as follows: (1) patients over 19 years of age; (2) histologically- or cytologically-proven pancreatic adenocarcinoma; and (3) at least one measurable lesion in accordance with the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1^[18]. The exclusion criteria were as follows: (1) discontinued FOLFIRINOX for any reason before the first response evaluation; (2) dose adjustment in the first cycle other than 75% of the standard-dose; (3) did not start the first cycle of FOLFIRINOX in Severance Hospital; (4) diagnosed other active malignancy at the same time as PC diagnosis; (5) administered another agent in combination with FOLFIRINOX; and (6) regularly administered granulocyte colony stimulating factor (G-CSF) for primary prophylaxis. All patients who met the inclusion criteria and did not meet the exclusion criteria were identified. These patients were divided into sFOLFIRINOX and mFOLFIRINOX groups according to their starting dose of FOLFIRINOX.

Work-up and treatment

Pretreatment assessment was conducted for all patients. Appropriate imaging modalities were used for staging work-up, as needed. The specimen for histological or cytological confirmation of malignancy was obtained by endoscopic ultrasonography-guided fine needle aspiration, percutaneous biopsy, or exploratory laparotomy, as indicated. For each patient, the attending physician made a clinical decision on whether the first cycle should be initiated with sFOLFIRINOX or mFOLFIRINOX. sFOLFIRINOX comprised a 2 h intravenous infusion (IVF) of oxaliplatin 85 mg/m², followed by a 90 min IVF of irinotecan 180 mg/m². FA 400 mg/m² IVF was performed over 2 h after termination of irinotecan infusion. This was followed by a 5-FU 400 mg/m² bolus and 2400 mg/m² IVF for 46 h. Patients who received a standard dose at the first cycle were grouped as sFOLFIRINOX. Patients who started with a 75% of standard-dose based on the decision of the attending physician were grouped as mFOLFIRINOX. All patients were regularly administered 0.25 mg of palonosetron 30 min before oxaliplatin infusion for emesis prophylaxis. G-CSF was not used for primary prophylaxis of neutropenia, and was administered when grade three or four neutropenia or neutropenic fever occurred. FOLFIRINOX was repeated every 2 wk until evidence of progressive disease (PD), significant deterioration of patient condition, or patient unwillingness. Dose reduction or delay was at the treating physician's discretion and fully considered if the patient

did not appear to tolerate the dosage of the previous cycle.

Assessment of treatment efficacy

Primary endpoints of this study were objective response rate (ORR) and disease control rate (DCR). Secondary endpoints were progression-free survival (PFS) and overall survival (OS). Treatment response was evaluated after every four cycles using computed tomography or magnetic resonance image. All imaging modalities were conducted and reviewed in compliance with the institutional standard protocols. According to the RECIST, responses were reported by a professional radiologist, and the final assessment was independently made by each attending physician. The best treatment response of each patient was recorded. The ORR included the rate of complete response (CR) and partial response (PR), while DCR was defined as a sum of ORR and the rate of stable disease (SD). For survival analysis, the patient's survival status, date of death, and date of last follow-up were recorded. The cut-off date of both survival and follow-up data was February 6, 2018. PFS was defined from the date of initiation of FOLFIRINOX to PD or death. The patients who survived and remained without PD were censored at the date of the last follow-up. Patients who missed a follow-up without PD and with < a 6-mo follow-up period were censored at 6 mo from treatment initiation, even if deaths were confirmed after that. If a treatment switch occurred without PD, such as curative resection, irreversible electroporation, or another chemotherapeutic regimen, the date of switching treatment was considered as the censoring point. OS was always defined from the date of initiation of FOLFIRINOX to death. Patients whose deaths were not confirmed were censored at the date of the last follow-up.

Assessment of adverse events

Treatment-related AE was also included in the secondary endpoints of this study. During the period of chemotherapy, treatment-related adverse events (AEs) were monitored and recorded by the attending physicians at each visit. All of the patients' medical records on AEs were reviewed. The assessment of AEs was carried out in conformity with the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03^[19]. AEs leading to dose-reduction or dose-delay were recorded separately.

Statistical analysis

For comparing the variables of both groups, Mann-Whitney test was used for continuous variables and Pearson's χ^2 test or Fisher's exact test were used for categorical variables. For the analysis of survival data, the Kaplan-Meier method was used to estimate the median survival with a 95% confidence interval (CI) and the log-rank test was used for comparison. A

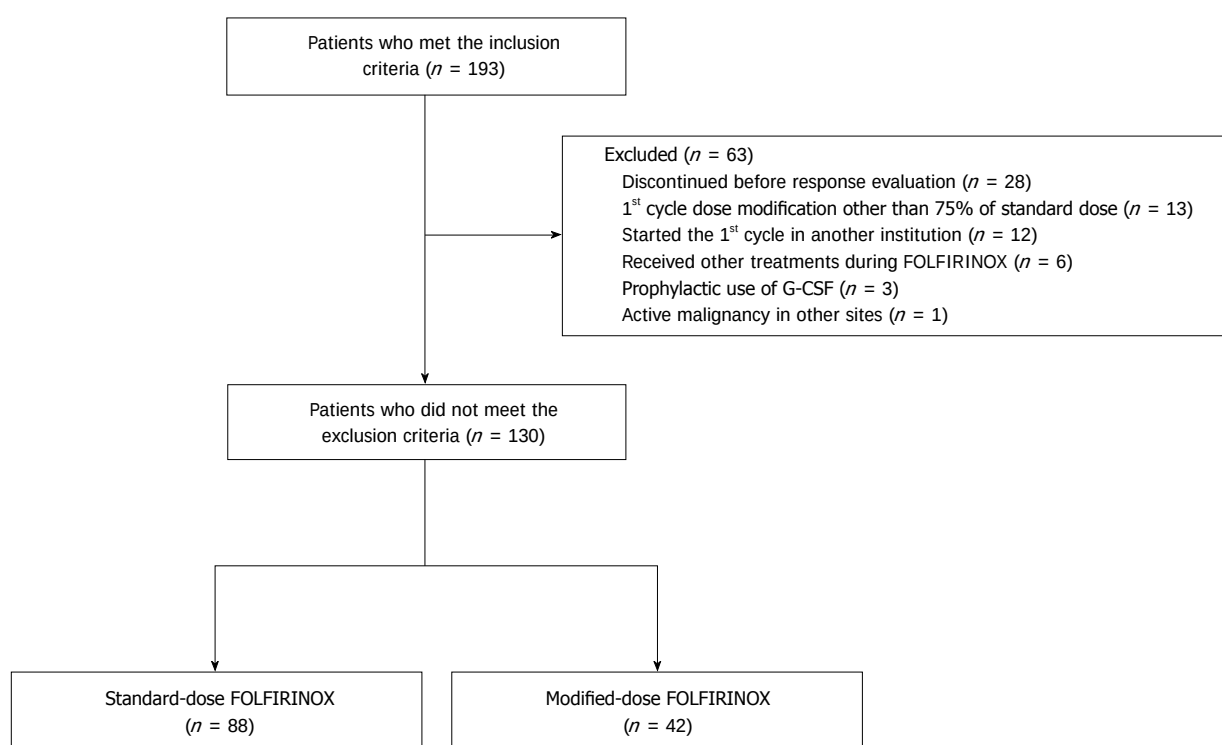


Figure 1 Flow chart of patient selection. G-CSF: granulocyte colony stimulating factor.

Cox proportional-hazards model was used to estimate the adjusted hazard ratios (HR). P -value < 0.05 was considered statistically significant. All statistical analyses were performed with IBM SPSS (version 23.0, IBM Corp., Armonk, NY, United States).

RESULTS

Patients and pretreatment characteristics

In total, 130 patients were included in the final analysis based on the inclusion and exclusion criteria. Of the 130 patients, 88 were assigned to the sFOLFIRINOX group and 42 patients were assigned to the mFOLFIRINOX group. The detailed flow chart of patient selection is shown in Figure 1. When comparing the pretreatment characteristics, the mFOLFIRINOX group included more female patients (30.7% vs 57.1%; $P = 0.004$) and older patients [age (median), 57 vs 63.5; $P = 0.018$] than the sFOLFIRINOX group (Table 1). Other characteristics did not differ between the two groups.

Treatment characteristics

The treatment characteristics are summarized in Table 2. The number of cycles administered and treatment duration were not different between the two groups. The median relative dose intensities (RDIs) of each of the four agents were significantly higher in the sFOLFIRINOX group than in the mFOLFIRINOX group. The proportion of patients who experienced dose-reduction after the first cycle was larger in the sFOLFIRINOX group than in the mFOLFIRINOX group

(70.5% vs 38.1%; $P < 0.001$); however, the rate of dose delay was not different between the two groups. Dose reduction due to neutropenia was higher in the sFOLFIRINOX group (60.2% vs 21.4%; $P < 0.001$), and, therefore, more patients were administered G-CSF (81.8% vs 64.3%; $P = 0.028$) and more G-CSF administrations were performed during the treatment period [3.5 times (range: 0-24) vs 2 times (range: 0-12); $P = 0.043$] than in the mFOLFIRINOX group.

Treatment responses and survivals

The ORR and DCR (primary end-points of this study) were not different between the two groups (Table 3). The median duration of follow-up was 10.3 mo in the sFOLFIRINOX group and 11.1 mo in the mFOLFIRINOX group ($P = 0.181$). The estimated median PFS of both groups were not different [sFOLFIRINOX: 8.7 mo (95%CI: 6.4-11.0) vs mFOLFIRINOX: 8.1 mo (95%CI: 6.7-9.6), $P = 0.272$] (Figure 2A). The estimated median OS of the sFOLFIRINOX group was 13.9 mo (95%CI: 11.5-16.4), and it was not different from that of the mFOLFIRINOX group [13.7 mo (95%CI: 9.5-17.9), $P = 0.476$] (Figure 2B). Additionally, age and sex-adjusted HRs of the mFOLFIRINOX group to the sFOLFIRINOX group were not statistically significant [HR for disease progression or death, 1.36 (95%CI: 0.81-2.26), $P = 0.242$; HR for death, 0.94 (95%CI: 0.55-1.60), $P = 0.813$].

Treatment-related AEs

Severe (grade three or higher) treatment-related AEs

Table 1 Pretreatment characteristics

	sFOLFIRINOX (<i>n</i> = 88)	mFOLFIRINOX (<i>n</i> = 42)	<i>P</i> value
Sex, <i>n</i> (%)			
Male	61 (69.3)	18 (42.9)	0.004 ¹
Female	27 (30.7)	24 (57.1)	
Age, yr			0.018 ¹
Median (range)	57 (31-79)	63.5 (41-77)	
ECOG-PS, <i>n</i> (%)			0.426
0	68 (77.3)	35 (83.3)	
1	20 (22.7)	7 (16.7)	
Laboratory test results, median (range)			
Absolute neutrophil count, / μ L	4200 (1610-11170)	4525 (2080-18930)	0.317
Hemoglobin, g/dL	12.3 (7.1-17.1)	12.1 (8.5-14.9)	0.36
Platelet count, $\times 10^3$ / μ L	218 (76-439)	245 (107-764)	0.247
Total bilirubin, mg/dL	0.7 (0.2-4.8)	0.5 (0.2-2.7)	0.144
Albumin, g/dL	3.9 (2.8-5.0)	3.9 (2.4-4.8)	0.797
Creatinine, mg/dL	0.67 (0.37-1.02)	0.70 (0.37-1.04)	0.516
Level of CA 19-9			
U/mL, median (range)	172.2 (0.6-20000.0)	455.5 (0.7-20000.0)	0.709
Normal, <i>n</i> (%)	17 (19.3)	11 (21.5)	0.274
Elevated, < 59 $\times$ ULN, <i>n</i> (%)	53 (60.2)	19 (45.2)	
Elevated, $\geq 59 \times$ ULN, <i>n</i> (%)	18 (20.5)	12 (28.6)	
Biliary drainage, <i>n</i> (%)			0.435
Presence	29 (33.0)	11 (26.2)	
Tumor location in pancreas, <i>n</i> (%)			0.657
Head	40 (45.5)	16 (38.1)	
Body and tail	44 (50.0)	23 (54.8)	
Recurrent	4 (4.5)	3 (7.1)	
Tumor size, cm			0.313
Median (range)	3.6 (1.3-7.7)	4.0 (1.3-8.0)	
Disease extent, <i>n</i> (%)			0.243
Borderline resectable	17 (19.3)	6 (14.3)	
Locally advanced	26 (29.5)	8 (19.0)	
Metastatic	45 (51.1)	28 (66.7)	
Stage, <i>n</i> (%)			0.248
II	24 (27.3)	8 (19.0)	
III	19 (21.6)	6 (14.3)	
IV	45 (51.1)	28 (66.7)	
Prior treatment, <i>n</i> (%)			0.941
Naïve	75 (85.2)	33 (85.7)	
Curative resection	4 (4.5)	4 (9.5)	
CCRT	9 (10.2)	4 (9.5)	1.000

¹Values indicate statistical significance. mFOLFIRINOX: Modified FOLFIRINOX; sFOLFIRINOX: Standard FOLFIRINOX; ECOG-PS: Eastern Cooperative Oncology Group performance status; ULN: Upper limit of normal range; CA: Carbohydrate antigen; CCRT: Concurrent chemoradiotherapy.

in the two groups are listed and compared in Table 4. Of the hematologic AEs, the rate of severe neutropenia was significantly lower in the mFOLFIRINOX group than in the sFOLFIRINOX group (83.0% vs 66.7%; $P = 0.044$). Other hematologic AE rates, including febrile neutropenia, were not different. Severe anorexia and diarrhea occurred less frequently in the mFOLFIRINOX group than in the sFOLFIRINOX group (48.9% vs 28.6%; $P = 0.029$; 13.6% vs 0.0%; $P = 0.009$; respectively). All other non-hematologic severe AEs tended to occur less frequently in the mFOLFIRINOX group, with the exception of lung infection.

DISCUSSION

In this study, we aimed to retrospectively compare the therapeutic efficacy and safety of sFOLFIRINOX

and mFOLFIRINOX as first-line chemotherapies for PC. To the best of our knowledge, this is the first direct comparative study that evaluated the efficacy and safety of sFOLFIRINOX and mFOLFIRINOX within a single institution. We observed that the median cycle and median duration of FOLFIRINOX were not different in both groups. Although the median RDI of all four agents were significantly less in the mFOLFIRINOX group, the therapeutic parameters such as ORR, DCR, OS, and PFS were not different between the two groups. Regarding the treatment-related AE profiles, severe neutropenia, anorexia, and diarrhea were remarkably lower in the mFOLFIRINOX group than in the sFOLFIRINOX group. Therefore, our study supports dose modification from the initiation of treatment without compromising treatment efficacy, particularly in elderly and female patients, who tend to show more

Table 2 Treatment characteristics

	sFOLFIRINOX (<i>n</i> = 88)	mFOLFIRINOX (<i>n</i> = 42)	<i>P</i> value
Number of cycles administered, median (range)	9.5 (4-24)	12 (4-32)	0.421
Treatment duration, d, median (range)	126 (42-322)	154 (42-434)	0.595
RDI to sFOLFIRINOX, %, median (range)			
Oxaliplatin	85.3 (56.3-100)	75.0 (51.1-75.0)	< 0.001 ¹
Irinotecan	85.0 (56.3-100)	75.0 (51.1-75.0)	< 0.001 ¹
5-FU (bolus)	92.1 (21.4-100)	75.0 (51.1-75.0)	< 0.001 ¹
5-FU (infusion)	94.1 (56.3-100)	75.0 (51.1-75.0)	< 0.001 ¹
Patients with ≥ 1 dose reduction, <i>n</i> (%)	62 (70.5)	16 (38.1)	< 0.001 ¹
Cause of dose reduction (> 5%), <i>n</i> (%)			
Neutropenia	53 (60.2)	9 (21.4)	< 0.001 ¹
Febrile neutropenia	10 (11.4)	4 (9.5)	1.000
Patients with ≥ 1 dose delay, <i>n</i> (%)	55 (62.5)	22 (52.4)	0.272
Cause of dose delay (> 5%), <i>n</i> (%)			
Neutropenia	16 (18.2)	5 (11.9)	0.363
Febrile neutropenia	16 (18.2)	5 (11.9)	0.363
Fatigue	7 (8.0)	8 (19.0)	0.081
No. of G-CSF administered, median (range)	3.5 (0-24)	2 (0-12)	0.043 ¹
Patients received G-CSF, <i>n</i> (%)	72 (81.8)	27 (64.3)	0.028 ¹

¹Values indicate statistical significance. mFOLFIRINOX: Modified FOLFIRINOX; sFOLFIRINOX: Standard FOLFIRINOX; RDI: Relative dose intensity; 5-FU: 5-Fluorouracil; G-CSF: Granulocyte colony-stimulating factor.

Table 3 Response evaluation *n* (%)

	sFOLFIRINOX (<i>n</i> = 88)	mFOLFIRINOX (<i>n</i> = 42)	<i>P</i> value
CR	1 (1.1)	1 (2.4)	
PR	34 (38.6)	14 (33.3)	
SD	36 (40.9)	20 (47.6)	
PD	17 (19.3)	7 (16.7)	
Objective response ^a	35 (39.8)	15 (35.7)	0.656
Disease control ^b	71 (80.7)	35 (83.3)	0.716

^aObjective response includes CR and PR; ^bDisease control includes CR, PR, and SD. mFOLFIRINOX: Modified FOLFIRINOX; sFOLFIRINOX: Standard FOLFIRINOX; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease.

concern about treatment-related toxicities.

Currently, FOLFIRINOX is a universally-used first-line treatment for MPC^[20,21], and it is also used for second-line or neoadjuvant treatment. Owing to its severe toxicities (grade ≥ 3 neutropenia in 45.7% of patients; grade ≥ 3 fatigue in 23.6% of patients) reported in the PRODIGE4/ACCORD11 trial^[7], treatment-related AE is a major concern when using FOLFIRINOX.

To reduce FOLFIRINOX-related toxicities, several groups have conducted studies focused on dose modification of FOLFIRINOX from the first cycle. Most of the FOLFIRINOX dose-modifying studies compared their results with the PRODIGE4/ACCORD11 trial. Retrospective research conducted in the UK using a reduced dose of irinotecan and omitting a 5-FU bolus reported a markedly lower rate of severe neutropenia than that in the historical trial, with similar rates of other severe AEs^[15]. In a US phase II trial using reduced doses of irinotecan and 5-FU bolus, the rates of severe neutropenia and vomiting were significantly lower than the rates in the historical trial; however, other severe AEs were similar^[17]. The toxicity of mFOLFIRINOX in this

study was less severe than sFOLFIRINOX. In addition, compared with that of the historical trial, the rate of severe diarrhea was lower, but the rates of severe neutropenia, febrile neutropenia, anemia, and vomiting were still higher in the mFOLFIRINOX.

Regarding neutropenia, 77.8% of patients experienced severe neutropenia in a Japanese phase II study of sFOLFIRINOX for chemotherapy-naïve MPC, which is similar to our study's findings^[22]. In addition, most studies conducted in Asian countries reported severe neutropenia in > 65% of patients^[23-26], which was more frequent than that in reports from western countries (11.0%-45.7%)^[7,27-29]. These results suggest that Asians may be prone to severe FOLFIRINOX-related neutropenia, and dose adjustment is an option that should be considered when treating patients belonging to the Asian population. Unlike the present study, prophylactic G-CSF was routinely administered at every cycle in the aforementioned studies focusing on dose modification of FOLFIRINOX^[13-17]. This distinction in therapeutic protocols should be considered when interpreting and comparing the rates of severe

Table 4 Adverse events ($\geq$ Grade 3) *n* (%)

Event	sFOLFIRINOX (<i>n</i> = 88)	mFOLFIRINOX (<i>n</i> = 42)	<i>P</i> value
Hematologic			
Neutropenia	73 (83.0)	28 (66.7)	0.044 ¹
Febrile neutropenia	24 (27.3)	9 (21.4)	0.474
Anemia	19 (21.6)	11 (26.2)	0.561
Thrombocytopenia	8 (9.1)	2 (4.8)	0.499
Non-hematologic			
Fatigue	33 (37.5)	14 (33.3)	0.644
Anorexia	43 (48.9)	12 (28.6)	0.029 ¹
Nausea/Vomiting	53 (60.2)	19 (45.2)	0.108
Diarrhea	12 (13.6)	0 (0.0)	0.009 ¹
Peripheral sensory neuropathy	12 (13.6)	2 (4.8)	0.224
Sepsis	5 (5.7)	0 (0.0)	0.174
Lung infection	3 (3.4)	4 (9.5)	0.212
Biliary tract infection	6 (6.8)	0 (0.0)	0.176

¹Values indicate statistical significance. mFOLFIRINOX: Modified FOLFIRINOX; sFOLFIRINOX: Standard FOLFIRINOX.

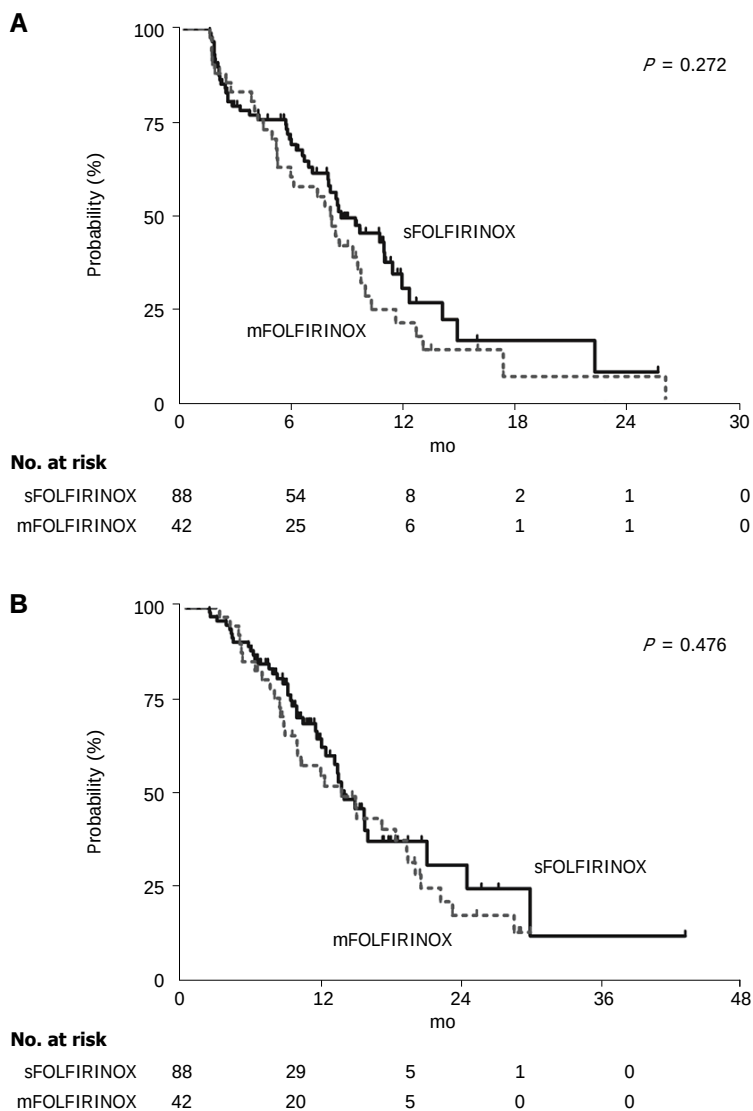


Figure 2 Survival analyses and comparisons. A: Progression-free survival; B: Overall survival, according to the treatment group. mFOLFIRINOX: Modified FOLFIRINOX; sFOLFIRINOX: Standard FOLFIRINOX.

neutropenia and neutropenic fever associated with mFOLFIRINOX in our study with those of prior research (67.9% vs 0%-12%; 26.4% vs 0%-5.6%; respectively).

Regarding efficacy, previous studies using a modified form of FOLFIRINOX showed 17.2%-46.7% of ORR and 80%-100% of DCR, which were similar to those of the PRODIGE4/ACCORD11 trial^[13,15,17]. Our modification of FOLFIRINOX with 75% of the standard-dose was able to markedly reduce toxicity, and the efficacy was comparable with that of sFOLFIRINOX or previous studies, including the PRODIGE4/ACCORD11 trial. This therefore suggests that, in our study population, dose modification to reduce toxicity is possible without compromising treatment efficacy.

There are certain limitations to this study. First, it has a retrospective study design. Although we selected patients based on strict exclusion criteria, the possibility of selection bias and information bias remains. Second, we included patients with BRPC and unresectable PC. When comparing the survival data with other trials, this characteristic of the patient population should be considered. Third, more females and older patients were included in the mFOLFIRINOX group. These differences may be attributed to the clinical characteristics of the patient, based on whether or not the attending physician decides to administer mFOLFIRINOX from the first cycle. These differences may affect the treatment outcome. A previous study reported that female gender could positively predict response to FOLFIRINOX in patients with advanced PC^[30]. However, the prognostic significance of gender in PC remains controversial and warrants further evaluation^[31]. Despite these limitations, this study is meaningful because it directly compares the two study groups, which underwent similar clinical practice within a single institution.

In conclusion, mFOLFIRINOX showed comparable efficacy to sFOLFIRINOX, with a better toxicity profile. Given the relatively high toxicity of sFOLFIRINOX, initiating FOLFIRINOX treatment, if clinically required, with 75% of the standard-dose can be an appropriate option to reduce toxicity concerns without compromising efficacy.

ARTICLE HIGHLIGHTS

Research background

Although FOLFIRINOX is one of the universally-used chemotherapies for pancreatic cancer, its relatively high rate of adverse events is still a major concern. Several studies suggest that dose-modified FOLFIRINOX (mFOLFIRINOX) can improve safety with comparable efficacy compared to the standard FOLFIRINOX (sFOLFIRINOX). However, clinical feasibility and the optimal strategy of mFOLFIRINOX remains unclear.

Research motivation

Previous studies on mFOLFIRINOX made conclusions based on comparing their results to the results of historical phase III trials of FOLFIRINOX. To date, direct comparative studies between sFOLFIRINOX and mFOLFIRINOX for pancreatic cancer is lacking.

Research objectives

We directly compared the safety and efficacy of sFOLFIRINOX and

mFOLFIRINOX in a single study. This could help clarify the clinical applicability of mFOLFIRINOX.

Research methods

The medical records of 130 pancreatic cancer patients [sFOLFIRINOX ($n = 88$), mFOLFIRINOX ($n = 42$)] were retrospectively reviewed. The objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) were compared for efficacy analysis. Severe ($\geq$ grade three) adverse event (AE) rates of the two groups were compared for toxicity analysis.

Research results

Although the median relative dose intensities of each of the drugs were significantly lower in the mFOLFIRINOX group, the response rates and survival were not different between the two groups (ORR: 39.8% vs 35.7%, $P = 0.656$; DCR: 80.7% vs 83.3%, $P = 0.716$; PFS: 8.7 mo vs 8.1 mo, $P = 0.272$; OS: 13.9 mo vs 13.7 mo, $P = 0.476$). Severe AE rates, including neutropenia (83.0% vs 66.7%; $P = 0.044$), anorexia (48.9% vs 28.6%; $P = 0.029$), and diarrhea (13.6% vs 0.0%; $P = 0.009$), were significantly lower in the mFOLFIRINOX group.

Research conclusions

In this direct comparative retrospective study, mFOLFIRINOX showed comparable efficacy to sFOLFIRINOX, with a better toxicity profile. Given the relatively high toxicity of sFOLFIRINOX, initiating FOLFIRINOX treatment, if clinically required, with 75% of the standard-dose could be an appropriate option to reduce toxicity concerns without compromising efficacy.

Research perspectives

In the future, prospective comparative studies need to be conducted to determine the optimal dose modification of FOLFIRINOX and who will benefit from this strategy.

REFERENCES

- 1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin* 2017; **67**: 7-30 [PMID: 28055103 DOI:10.3322/caac.21387]
- 2 Jung KW, Won YJ, Oh CM, Kong HJ, Lee DH, Lee KH; Community of Population-Based Regional Cancer Registries. Cancer Statistics in Korea: Incidence, Mortality, Survival, and Prevalence in 2014. *Cancer Res Treat* 2017; **49**: 292-305 [PMID: 28279062 DOI: 10.4143/crt.2017.118]
- 3 Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997; **15**: 2403-2413 [PMID: 9196156 DOI: 10.1200/jco.1997.15.6.2403]
- 4 Heinemann V, Quetzsch D, Gieseler F, Gonnermann M, Schönekeas H, Rost A, Neuhaus H, Haag C, Clemens M, Heinrich B, Vehling-Kaiser U, Fuchs M, Fleckenstein D, Gesierich W, Uthgenannt D, Einsele H, Holstege A, Hinke A, Schalhorn A, Wilkowski R. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol* 2006; **24**: 3946-3952 [PMID: 16921047 DOI: 10.1200/jco.2005.05.1490]
- 5 Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, Campos D, Lim R, Ding K, Clark G, Voskoglou-Nomikos T, Ptasynski M, Parulekar W; National Cancer Institute of Canada Clinical Trials Group. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007; **25**: 1960-1966 [PMID: 17452677 DOI: 10.1200/jco.2006.07.9525]
- 6 Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero

- J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369**: 1691-1703 [PMID: 24131140 DOI: 10.1056/NEJMoa1304369]
- 7 **Conroy T**, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécauarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bannoun J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; **364**: 1817-1825 [PMID: 21561347 DOI: 10.1056/NEJMoa1011923]
 - 8 **Petrelli F**, Cohn A, Borgonovo K, Cabiddu M, Ghilardi M, Lonati V, Aitini E, Barni S; Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente (GISCAD). FOLFIRINOX-based neoadjuvant therapy in borderline resectable or unresectable pancreatic cancer: a meta-analytical review of published studies. *Pancreas* 2015; **44**: 515-521 [PMID: 25872127 DOI: 10.1097/MPA.0000000000000314]
 - 9 **Suker M**, Beumer BR, Sadot E, Marthey L, Faris JE, Mellon EA, El-Rayes BF, Wang-Gillam A, Lacy J, Hosein PJ, Moorcraft SY, Conroy T, Hohl F, Allen P, Taieb J, Hong TS, Shridhar R, Chau I, van Eijck CH, Koerkamp BG. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. *Lancet Oncol* 2016; **17**: 801-810 [PMID: 27160474 DOI: 10.1016/S1470-2045(16)00172-8]
 - 10 **Ducreux M**, Cuhna AS, Caramella C, Hollebecque A, Burtin P, Goéré D, Seufferlein T, Haustermans K, Van Laethem JL, Conroy T, Arnold D; ESMO Guidelines Committee. Cancer of the pancreas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2015; **26** Suppl 5: v56-v68 [PMID: 26314780 DOI: 10.1093/annonc/mdv295]
 - 11 **Sohal DP**, Mangu PB, Khorana AA, Shah MA, Philip PA, O'Reilly EM, Uronis HE, Ramanathan RK, Crane CH, Engebretson A, Ruggiero JT, Copur MS, Lau M, Urba S, Laheru D. Metastatic Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2016; **34**: 2784-2796 [PMID: 27247222 DOI: 10.1200/JCO.2016.67.1412]
 - 12 **Tempero MA**, Malafa MP, Al-Hawary M, Asbun H, Bain A, Behrman SW, Benson AB 3rd, Binder E, Cardin DB, Cha C, Chiorean EG, Chung V, Czito B, Dillhoff M, Dotan E, Ferrone CR, Hardacre J, Hawkins WG, Herman J, Ko AH, Komanduri S, Koong A, LoConte N, Lowy AM, Moravek C, Nakakura EK, O'Reilly EM, Obando J, Reddy S, Scaife C, Thayer S, Weekes CD, Wolff RA, Wolpin BM, Burns J, Darlow S. Pancreatic Adenocarcinoma, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2017; **15**: 1028-1061 [PMID: 28784865 DOI: 10.6004/jnccn.2017.0131]
 - 13 **Mahaseeth H**, Brucher E, Kauh J, Hawk N, Kim S, Chen Z, Kooby DA, Maithel SK, Landry J, El-Rayes BF. Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. *Pancreas* 2013; **42**: 1311-1315 [PMID: 24152956 DOI: 10.1097/MPA.0b013e31829e2006]
 - 14 **Blazer M**, Wu C, Goldberg RM, Phillips G, Schmidt C, Muscarella P, Wuthrick E, Williams TM, Reardon J, Ellison EC, Bloomston M, Bekaii-Saab T. Neoadjuvant modified (m) FOLFIRINOX for locally advanced unresectable (LAPC) and borderline resectable (BRPC) adenocarcinoma of the pancreas. *Ann Surg Oncol* 2015; **22**: 1153-1159 [PMID: 25358667 DOI: 10.1245/s10434-014-4225-1]
 - 15 **Ghorani E**, Wong HH, Hewitt C, Calder J, Corrie P, Basu B. Safety and Efficacy of Modified FOLFIRINOX for Advanced Pancreatic Adenocarcinoma: A UK Single-Centre Experience. *Oncology* 2015; **89**: 281-287 [PMID: 26372905 DOI: 10.1159/000439171]
 - 16 **Nanda RH**, El-Rayes B, Maithel SK, Landry J. Neoadjuvant modified FOLFIRINOX and chemoradiation therapy for locally advanced pancreatic cancer improves resectability. *J Surg Oncol* 2015; **111**: 1028-1034 [PMID: 26073887 DOI: 10.1002/jso.23921]
 - 17 **Stein SM**, James ES, Deng Y, Cong X, Kortmansky JS, Li J, Staugaard C, Indukala D, Boustani AM, Patel V, Cha CH, Salem RR, Chang B, Hochster HS, Lacy J. Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer. *Br J Cancer* 2016; **114**: 737-743 [PMID: 27022826 DOI: 10.1038/bjc.2016.45]
 - 18 **Eisenhauer EA**, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228-247 [PMID: 19097774 DOI: 10.1016/j.ejca.2008.10.026]
 - 19 **National Cancer Institute**. Common Terminology Criteria for Adverse Events (CTCAE). v4.03. ed: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. 2010; Available from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/
 - 20 **Le N**, Vinci A, Schober M, Krug S, Javed MA, Kohlmann T, Sund M, Neesse A, Beyer G. Real-World Clinical Practice of Intensified Chemotherapies for Metastatic Pancreatic Cancer: Results from a Pan-European Questionnaire Study. *Digestion* 2016; **94**: 222-229 [PMID: 28030863 DOI: 10.1159/000453257]
 - 21 **Abrams TA**, Meyer G, Meyerhardt JA, Wolpin BM, Schrag D, Fuchs CS. Patterns of Chemotherapy Use in a U.S.-Based Cohort of Patients with Metastatic Pancreatic Cancer. *Oncologist* 2017; **22**: 925-933 [PMID: 28476943 DOI: 10.1634/theoncologist.2016-0447]
 - 22 **Okusaka T**, Ikeda M, Fukutomi A, Ioka T, Furuse J, Ohkawa S, Isayama H, Boku N. Phase II study of FOLFIRINOX for chemotherapy-naïve Japanese patients with metastatic pancreatic cancer. *Cancer Sci* 2014; **105**: 1321-1326 [PMID: 25117729 DOI: 10.1111/cas.12501]
 - 23 **Kobayashi N**, Shimamura T, Tokuhisa M, Goto A, Endo I, Ichikawa Y. Effect of FOLFIRINOX as second-line chemotherapy for metastatic pancreatic cancer after gemcitabine-based chemotherapy failure. *Medicine* (Baltimore) 2017; **96**: e6769 [PMID: 28489753 DOI: 10.1097/MD.00000000000006769]
 - 24 **Muranaka T**, Kuwatani M, Komatsu Y, Sawada K, Nakatsumi H, Kawamoto Y, Yuki S, Kubota Y, Kubo K, Kawahata S, Kawakubo K, Kawakami H, Sakamoto N. Comparison of efficacy and toxicity of FOLFIRINOX and gemcitabine with nab-paclitaxel in unresectable pancreatic cancer. *J Gastrointest Oncol* 2017; **8**: 566-571 [PMID: 28736643 DOI: 10.21037/jgo.2017.02.02]
 - 25 **Yoo C**, Kang J, Kim KP, Lee JL, Ryoo BY, Chang HM, Lee SS, Park DH, Song TJ, Seo DW, Lee SK, Kim MH, Park JH, Hwang DW, Song KB, Lee JH, Kim SC. Efficacy and safety of neoadjuvant FOLFIRINOX for borderline resectable pancreatic adenocarcinoma: improved efficacy compared with gemcitabine-based regimen. *Oncotarget* 2017; **8**: 46337-46347 [PMID: 28564637 DOI: 10.18632/oncotarget.17940]
 - 26 **Yoshida K**, Iwashita T, Uemura S, Maruta A, Okuno M, Ando N, Iwata K, Kawaguchi J, Mukai T, Shimizu M. A multicenter prospective phase II study of first-line modified FOLFIRINOX for unresectable advanced pancreatic cancer. *Oncotarget* 2017; **8**: 111346-111355 [PMID: 29340058 DOI: 10.18632/oncotarget.22795]
 - 27 **Marthey L**, Sa-Cunha A, Blanc JF, Gauthier M, Cuffe A, Francois E, Trouilloud I, Malka D, Bachet JB, Coriat R, Terreboune E, De La Fouchardière C, Manfredi S, Solub D, Lécaille C, Thiot Bidault A, Carbonnel F, Taieb J. FOLFIRINOX for locally advanced pancreatic adenocarcinoma: results of an AGE0 multicenter prospective observational cohort. *Ann Surg Oncol* 2015; **22**: 295-301 [PMID: 25037971 DOI: 10.1245/s10434-014-3898-9]
 - 28 **Chilamma MK**, Cook N, Dhani NC, Giby K, Dodd A, Wang L, Hedley DW, Moore MJ, Knox JJ. FOLFIRINOX for advanced pancreatic cancer: the Princess Margaret Cancer Centre experience. *Br J Cancer* 2016; **115**: 649-654 [PMID: 27467054 DOI: 10.1038/bjc.2016.222]
 - 29 **Faris JE**, Blaszkowsky LS, McDermott S, Guimaraes AR, Szymonifka J, Huynh MA, Ferrone CR, Wargo JA, Allen JN, Dias

- LE, Kwak EL, Lillemoe KD, Thayer SP, Murphy JE, Zhu AX, Sahani DV, Wo JY, Clark JW, Fernandez-del Castillo C, Ryan DP, Hong TS. FOLFIRINOX in locally advanced pancreatic cancer: the Massachusetts General Hospital Cancer Center experience. *Oncologist* 2013; **18**: 543-548 [PMID: 23657686 DOI: 10.1634/theoncologist.2012-0435]
- 30 **Hohla F**, Hopfinger G, Romeder F, Rinnerthaler G, Bezan A, Stättner S, Hauser-Kronberger C, Ulmer H, Greil R. Female gender may predict response to FOLFIRINOX in patients with unresectable pancreatic cancer: a single institution retrospective review. *Int J Oncol* 2014; **44**: 319-326 [PMID: 24247204 DOI: 10.3892/ijo.2013.2176]
- 31 **Lambert A**, Jarlier M, Gourgou Bourgade S, Conroy T. Response to FOLFIRINOX by gender in patients with metastatic pancreatic cancer: Results from the PRODIGE 4/ ACCORD 11 randomized trial. *PLoS One* 2017; **12**: e0183288 [PMID: 28931010 DOI: 10.1371/journal.pone.0183288]
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Appendix KNOX01

PASS-01: Randomized Phase II Trial of Modified FOLFIRINOX Versus Gemcitabine/Nab-Paclitaxel and Molecular Correlatives for Previously Untreated Metastatic Pancreatic Cancer

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ABSTRACT

PURPOSE To assess modified folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin (FOLFIRINOX [mFFX]) versus gemcitabine/nab-paclitaxel (GnP) in de novo metastatic pancreatic ductal adenocarcinoma (PDAC) and explore predictive biomarkers.

PATIENTS AND METHODS Patients were randomly assigned 1:1 to mFFX or GnP with exclusion of germline pathogenic variants in *BRCA1/2* or *PALB2*. The primary end point was progression-free survival (PFS) between arms with 0.3 significance. The per-protocol (PP) population included patients who received one dose of chemotherapy. Pretreatment biopsies underwent whole-genome/transcriptome sequencing and patient-derived organoid (PDO) development, providing correlate recommendations at a molecular tumor board and outcomes assessed according to RNA signatures (basal-like v classical).

RESULTS Of 160 patients randomly assigned (80 mFFX, 80 GnP), 140 patients were in the PP population (71 mFFX, 69 GnP), with median follow-up of 8.3 months. The median PFS was 4.0 months for mFFX versus 5.3 months for GnP (hazard ratio [HR], 1.37 [95% CI, 0.97 to 1.92]; $P = .069$) in intention-to-treat. Median overall survival (OS) was 8.5 months with mFFX and 9.7 months with GnP (HR, 1.57 [95% CI, 1.08 to 2.28]; $P = .017$). Genomic data were generated in 94%, transcriptomes in 74%, and PDOs in 50%. The median PFS for those with basal-like was 3.0 (mFFX) and 5.5 (GnP) months ($P = .17$), and classical PDAC was 6.3 (mFFX) versus 5.4 (GnP) months ($P = .36$). The median OS in basal-like was 7.5 (mFFX) and 8.9 (GnP) months ($P = .75$) versus in classical OS was 9.7 (mFFX) and 13.9 (GnP) months ($P = .047$). Overall, 75 (54%) of patients received second-line treatment, 33/75 (44%) correlate-guided. The median time on second-line treatment was only 2.1 months with a median OS of 5.4 months for a correlate-guided choice versus 4.4 months on a standard chemotherapy approach ($P = .45$).

CONCLUSION In the phase II Pancreatic Adenocarcinoma Signature Stratification for Treatment-01 (PASS-01) trial population, PFS was similar between GnP and mFFX; however, OS and safety trends favored GnP. The second-line setting appears inadequate to offer precision choices, given the short survival observed.

ACCOMPANYING CONTENT

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 Appendix

 Data Sharing Statement

 Protocol

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy treated with combination chemotherapy.

Modified folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin (FOLFIRINOX [mFFX]) and gemcitabine/nab-paclitaxel (GnP) are standard treatment options for advanced PDAC.¹⁻³ Clinician judgment often dictates which

CONTEXT

Key Objective

In a randomized trial comparing survival outcomes between standard chemotherapies in metastatic pancreatic cancer, outcomes by subtype and correlatives were explored to further our understanding of the molecular determinants of response and resistance.

Knowledge Generated

In the first-line setting, patients with de novo metastatic cancer (*gBRCA/PALB2* excluded) had longer progression-free survival and overall survival with gemcitabine/nab-paclitaxel over modified FOLFIRINOX where outcomes were worse among basal-like subtypes. Despite extensive molecular profiling, only a few patients were able to benefit from precision choices in the second-line setting.

Relevance (A.H. Ko)

Molecular profiling of metastatic pancreatic cancer not only offers valuable prognostic information, but may even be potentially useful in helping guide selection of chemotherapy if such information can be obtained in a timely fashion.*

*Relevance section written by JCO Associate Editor Andrew H. Ko, MD, FASCO.

regimen is offered, as mFFX and GnP have not been prospectively compared in a randomized trial in North America.^{4,5} More recent data from the NAPOLI-3 trial favor NALIRIFOX (folinic acid/leucovorin, fluorouracil, liposomal-irinotecan, oxaliplatin) over GnP in unselected patients, offering another first-line option.⁶

PDAC is a genomically heterogeneous malignancy. Deleterious *BRCA2* and *PALB2* mutations are found in approximately 10–15% of patients⁷ and serve as predictive biomarkers of platinum and PARP inhibitor response, demonstrating that biomarker stratification in PDAC has clinical value. Transcriptomic profiling of PDAC has revealed two broad subtypes, classical and basal-like.⁸ In a prospective, biospecimen-based study of patients with PDAC treated in the first-line setting, objective response rates (ORRs) were significantly better in patients with the classical subtype compared with those with basal-like,⁹ suggesting the transcriptional subtypes may serve as a predictive biomarker. It has been previously shown that *GATA6* RNA in situ hybridization (ISH)¹⁰ has good concordance with RNA sequencing, a potential surrogate assay with clinical utility. In addition, signatures from patient-derived organoids (PDOs) also suggest biomarkers of sensitivity.¹¹

Pancreatic Adenocarcinoma Signature Stratification for Treatment-01 (PASS-01) was a prospective phase II, randomized, multinational clinical trial, comparing mFFX versus GnP in the first-line setting for patients with metastatic PDAC. The study objectives were to compare survival outcomes and to assess outcomes by subtype and molecular correlatives to further our understanding of the molecular determinants of response and resistance.

PATIENTS AND METHODS

Study Design and Participants

PASS-01 (ClinicalTrials.gov identifier: [NCT04469556](https://clinicaltrials.gov/ct2/show/study/NCT04469556)) enrolled patients age 18 years or older with metastatic PDAC, measurable disease per RECIST 1.1, and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. Eligibility consisted of patients with histologic or radiographic diagnosis of de novo untreated metastatic PDAC at screening with histology subsequently confirmed before random assignment. Patients were required to have a tumor lesion amenable to biopsy with at least four 18-gauge core needle samples. Histologic variants of mucinous adenocarcinoma or adenosquamous carcinoma were permitted. Patients with a known or strongly suspected germline mutation in *BRCA* or *PALB2* were excluded and treated off protocol as per standard of care. Enrollment occurred at six institutions: two in Canada and four in the United States.

Patients were randomly assigned (1:1) to receive mFFX or GnP, dosed as per institutional standard of care. Treatment continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met.

The final protocol, amendments, and patient informed consent documents were reviewed and approved by the institutional review boards and independent ethics committees at each site. All patients provided written informed consent. This study was conducted in compliance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice Guidelines.

End Points

The intention-to-treat (ITT) population consisted of all randomly assigned participants and the per-protocol (PP) population of evaluable patients consisted of patients who received at least one dose of assigned chemotherapy. The primary end point of the study was progression-free survival (PFS), defined as the time from random assignment to (first) progression according to RECIST (investigator assessed) or death, whichever earlier, or last follow-up when alive without progression. The secondary efficacy end points were ORR, duration of response (DOR) in the PP population, and overall survival (OS). Disease control rate (DCR) was defined as the rate of complete response (CR), partial response (PR), or stable disease (SD). DOR was defined as the duration from first PR or CR to progression or death, or to last follow-up if the patient was alive without progression at last follow-up. Safety was evaluated using National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0, of treatment-related serious adverse events (SAEs).

Biomarkers/Correlative Analysis and Molecular Tumor Board

Several hypotheses for biomarkers of chemotherapy regimens were explored and data discussed at molecular tumor boards (MTB). Biopsies were laser-captured microdissected for whole-genome and transcriptome sequencing (WGTS), and PDOs were derived as previously described.^{9,11} Whole genomes reported HRDetect scores available at MTB. Transcriptomic subtype was assessed using a tumor-enriched RNA signature derived by RNA sequencing.⁹ This was blinded to physicians at MTB until progression.

Clinical outcomes were analyzed by transcriptional subtype (basal-like or classical) and by *GATA6* expression as secondary end points. *GATA6* ISH expression was assessed on baseline histology slides¹⁰ and levels were dichotomized into high versus low.

Finally, treating with a biomarker-influenced second-line therapy versus an empiric standard of care was recorded by each investigator on the basis of the discussion during MTB focused on each patient. The monthly MTB consisted of all clinical and translational PASS-01 investigators and included presentation of correlative data and a review of existing relevant literature and potential for on-trial or off-label access to therapy. The choice for subsequent lines was the decision of the patient in discussion with the treating investigator, potentially using the information from MTB.

Exploratory end points included CA19-9 response, measured at the early time point of 4 weeks on chemotherapy. Detailed analysis of remaining exploratory end points including whole genome sequencing (WGS), transcriptomics, PDOs, CODEX immunoprofiling, circulating tumor cells, and

circulating tumor DNA (ctDNA) is ongoing and will be reported later.

Statistical Analyses

The sample size justification was based on the primary end point PFS. We estimated a total of 136 patients (68 per group) with a minimum of 112 events will achieve 80% power at a 0.3 significance level to detect a hazard ratio (HR) of 0.7 when the median PFS with mFFX was assumed to be approximately 7 months using two-sided log-rank test. Given the sample size was limited (funding and the clinical setting) and the need to maximize sensitivity/power for detecting a treatment signal, the relaxed two-sided alpha 0.3 (0.15 one side) was chosen to balance the risk of missing a potential efficacy signal for the design. The primary and secondary efficacy end points (PFS/OS) were analyzed on the basis of the ITT principle. The PP analyses were conducted for both primary and other secondary end points and subgroup analysis. The rate of PFS/OS were estimated using the Kaplan-Meier method and compared between the mFFX and GnP arms using log-rank test. HRs were reported with GnP as the reference, HR < 1 indicating mFFX was better, while HR > 1 indicates GnP better. Other secondary end points such as ORR, DOR, and SAEs were compared between two groups using chi-square test for categorical variables and Student t-test or Wilcoxon rank sum test for continuous variables. The association of PFS/OS with *GATA6* and CA19-9 were examined using similar methods. Subgroup analyses were conducted to examine the treatment effect in patient subgroups of interest using Cox proportional-hazard models with interaction term. However, because of the underpowering of these multiple exploratory end points, the focus was on the magnitude of difference in the treatment effect. Data management and all statistical analyses were performed using SAS 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Patient Characteristics and Enrollment

Between October 2020 and January 2024, 160 patients were enrolled and randomly assigned to receive mFFX (n = 80) or GnP (n = 80; Fig 1). Overall, patients had a median age of 64 years (range, 40-81), 63% were male, and 36% of the patients were non-White (Table 1). Demographic and baseline disease characteristics were generally balanced between groups, although the *KRAS* wildtype (WT) population and ECOG PS 0 was higher in the GnP group (14% v 4% and 59% v 41%, respectively), and somatic only biallelic *BRCA2* (2), *RAD51C* (2), and one with somatic homologous recombination deficiency (HRD) with no identifiable etiology were higher in the mFFX group (3% v 0.6%). However, in a Cox proportional-hazard regression analysis of potential baseline prognostic features, only the absence of liver metastasis appeared significant for better PFS and OS (data not shown). Of the PP population, 71 (89%) in the mFFX group and 69 (86%) in the GnP group were evaluable for PFS and

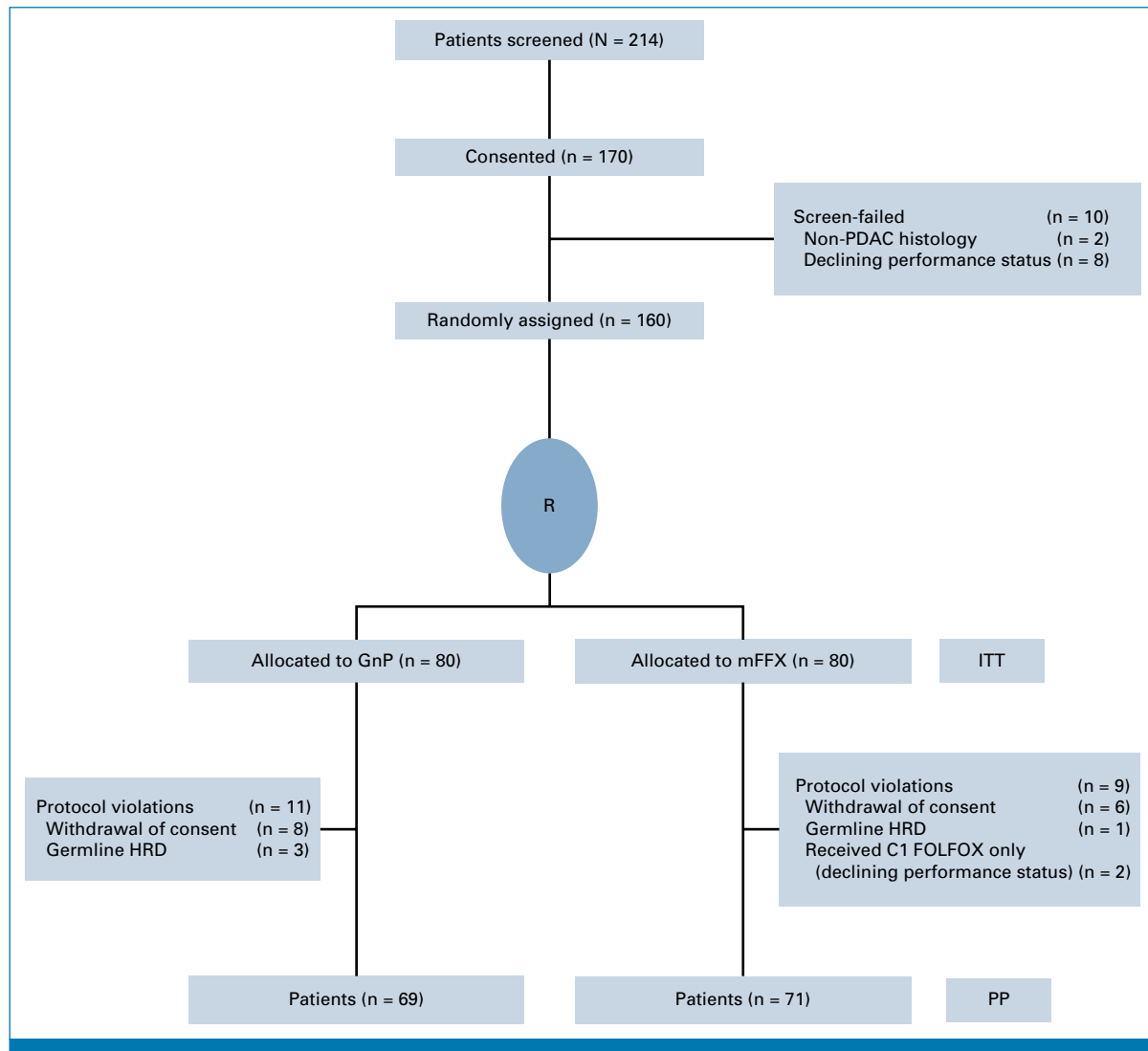


FIG 1. CONSORT diagram. FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; GnP, gemcitabine/nab-paclitaxel; HRD, homologous recombination deficiency; ITT, intention-to-treat; mFFX, modified FOLFIRINOX; PDAC, pancreatic ductal adenocarcinoma; PP, per-protocol

ORR. At data cutoff, 7 (5%) remained on first-line per arm, and 23 (33%) patients in the GnP group and 14 (20%) in the mFFX group were alive. Median follow-up on the study was 8.3 months as of August 31, 2024 (range, 0.3–37.2 months), with 8.2 months for GnP and 8.4 months for mFFX ($P = .24$). There were 143 PFS events in the ITT population and 130 PFS events among the 140 patients in the PP population.

Efficacy

For the ITT population, the median PFS was 4.0 months for mFFX and 5.3 months for GnP (HR, 1.37 [95% CI, 0.97 to 1.92]; $P = .069$; [Fig 2A](#)). Median OS was 8.5 months for mFFX versus 9.7 months for GnP (HR, 1.57 [95% CI, 1.08 to 2.28]; $P = .017$; [Fig 2B](#)). The median duration of PP first-line treatment was 3.7 months for mFFX versus 4.9 months for GnP. Median PFS was 4.2 months for mFFX compared with 5.3 months for GnP (HR, 1.33 [95% CI, 0.93 to 1.90]; $P = .114$).

Median OS was 8.7 months for mFFX compared with 10.3 months for GnP (HR, 1.59 [95% CI, 1.07 to 2.36]; $P = .021$; [Appendix Figs A1A and A1B](#), online only). After adjustment for potential confounders (ECOG PS, presence of liver metastasis, and *KRAS* WT status), the HR was reduced to 1.27 and 1.25 for PFS and OS, respectively ([Appendix Table A1](#)). There was no statistically significant difference in the treatment effect across baseline features, except better PFS for male gender and OS for absence of liver metastasis when treated with GnP ([Appendix Figs A2 and A3](#)).

The ORRs were 30% and 29% for GnP and mFFX, respectively ([Figs 3A and 3B](#)). DCR was higher in the GnP group compared with the mFFX group (79.7% v 62.9%, $P = .028$). Median time to RECIST response was 3.5 months in both arms. DOR favored GnP at 5.9 versus 4.7 months ($P = .025$). Patients with *KRAS* WT or somatic HRD tended to cluster with deeper responses.

TABLE 1. Characteristics of the Patient Population (intention-to-treat)

Patient Characteristic	Treatment		
	GnP (n = 80)	mFFX (n = 80)	All (N = 160)
Age at random assignment, years, mean (standard deviation)	64.6 (7.7)	62.6 (9.8)	63.6 (8.8)
Range	44.0-79.0	40.0-81.0	40.0-81.0
Sex, No. (%)			
Female	28 (35.0)	31 (38.8)	59 (36.9)
Male	52 (65.0)	49 (61.3)	101 (63.1)
BMI, median (range)	26.7 (18.8-44.3)	25.3 (17.6-42.8)	26.1 (17.6-44.3)
ECOG, No. (%)			
0	47 (58.8)	33 (41.3)	80 (50.0)
1	33 (41.3)	47 (58.8)	80 (50.0)
Race group, No. (%)			
Asian	7 (8.8)	15 (18.8)	22 (13.8)
Black or African American	10 (12.5)	5 (6.3)	15 (9.4)
White	56 (70.0)	46 (57.5)	102 (63.8)
Other	3 (3.8)	8 (10.0)	11 (6.9)
Unknown	4	6	10
Region, No. (%)			
Canada	37 (46.3)	35 (43.8)	72 (45.0)
United States	43 (53.8)	45 (56.3)	88 (55.0)
Histologic diagnosis			
Adenocarcinoma	77 (96.3)	75 (93.8)	152 (95.0)
Adenosquamous	0 (0.0)	1 (1.3)	1 (0.6)
Mucinous adenocarcinoma	1 (1.3)	1 (1.25)	2 (1.3)
Poorly differentiated carcinoma	2 (2.5)	3 (3.8)	5 (3.1)
CA 19-9 at baseline (U/mL), median (range)	1,292.0 (1.0-183,038.0)	1,628.3 (1.0-1,685,985.0)	1,454.5 (1.0-1,685,985.0)
Liver metastasis			
No	16 (20.0)	9 (11.4)	25 (15.7)
Yes	64 (80.0)	70 (88.6)	134 (84.3)
NA	0	1	1
Lung only metastasis	0	0	0
Transcriptional subtype, No. (%)			
Basal-like	13 (22.8)	19 (32.2)	32 (27.6)
Classical	44 (77.2)	40 (67.8)	84 (72.4)
NA	23	21	44
KRAS WT, No. (%)			
No	62 (86.1)	72 (96.0)	134 (91.2)
Yes	10 (13.9)	3 (4.0)	13 (8.8)
NA	8	5	13
Somatic HRD+, No. (%)			
No	79 (98.8)	76 (95.0)	155 (96.9)
Yes	1 (1.3)	4 (5.0)	5 (3.1)
GATA6 ISH, No. (%)			
High	42 (76.4)	48 (71.6)	90 (73.8)
Low	13 (23.6)	19 (28.4)	32 (26.2)
NA	25	13	38

Abbreviations: FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; HRD, homologous recombination deficiency; ISH, in situ hybridization; mFFX, modified FOLFIRINOX; NA, not available; WT, wildtype.

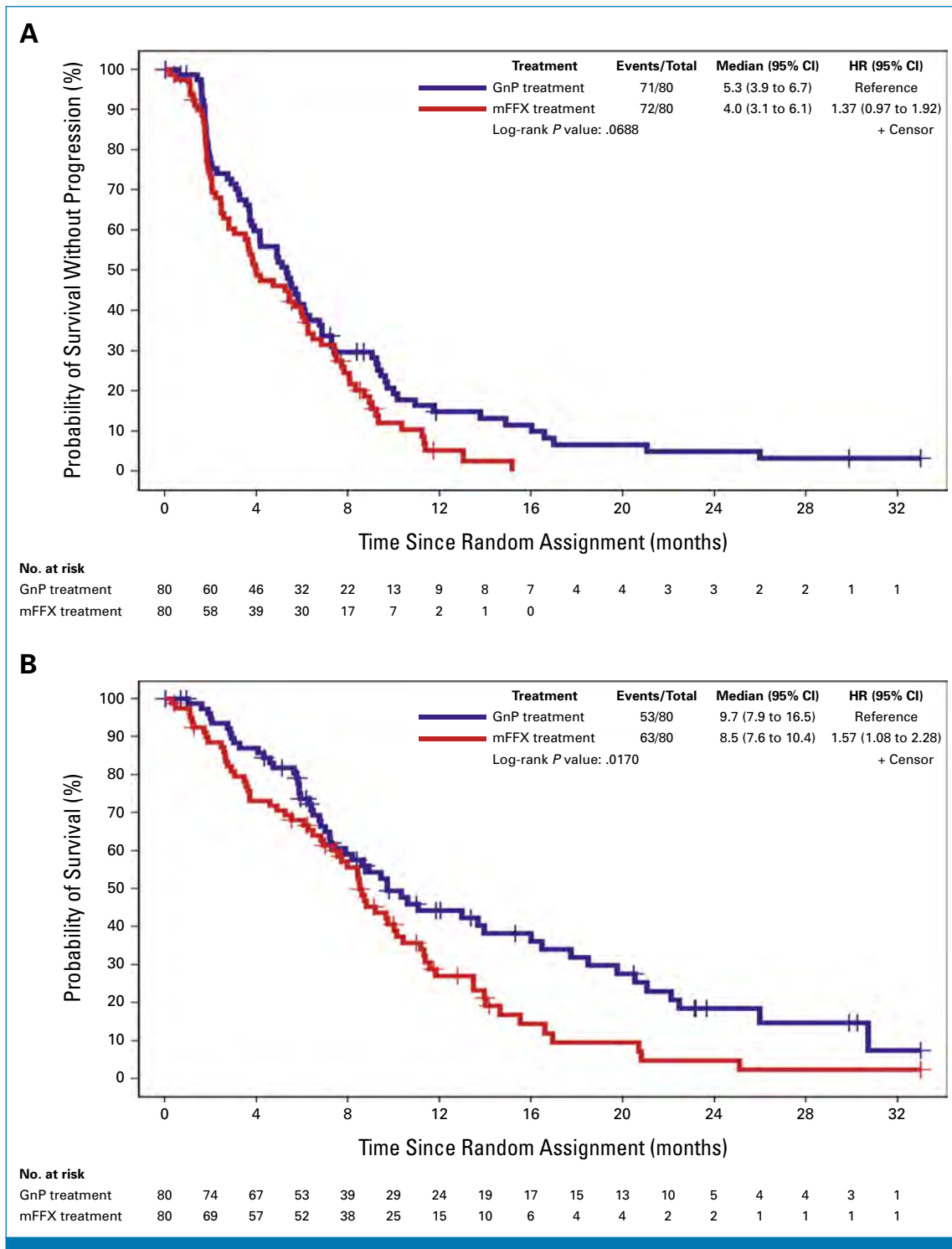


FIG 2. Comparison of (A) PFS and (B) OS between two treatment groups: mFFX and GnP treatment for ITT population (160 patients). FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; GnP, gemcitabine/nab-paclitaxel; HR, hazard ratio; ITT, intention-to-treat; mFFX, modified FOLFIRINOX; OS, overall survival; PFS, progression-free survival.

Safety

Given the chemotherapy regimens in this trial were established standards in PDAC with ample published toxicity data, to assess safety, we collected SAEs only. Hospital admissions

for clear treatment-related toxicities occurred as unique events in 14/71 (20%) patients on mFFX and 5/69 (7%) patients on GnP. Hospitalizations from mFFX were seven GI-related complications, three febrile neutropenia, and one each of pneumonia, acute renal failure, pulmonary

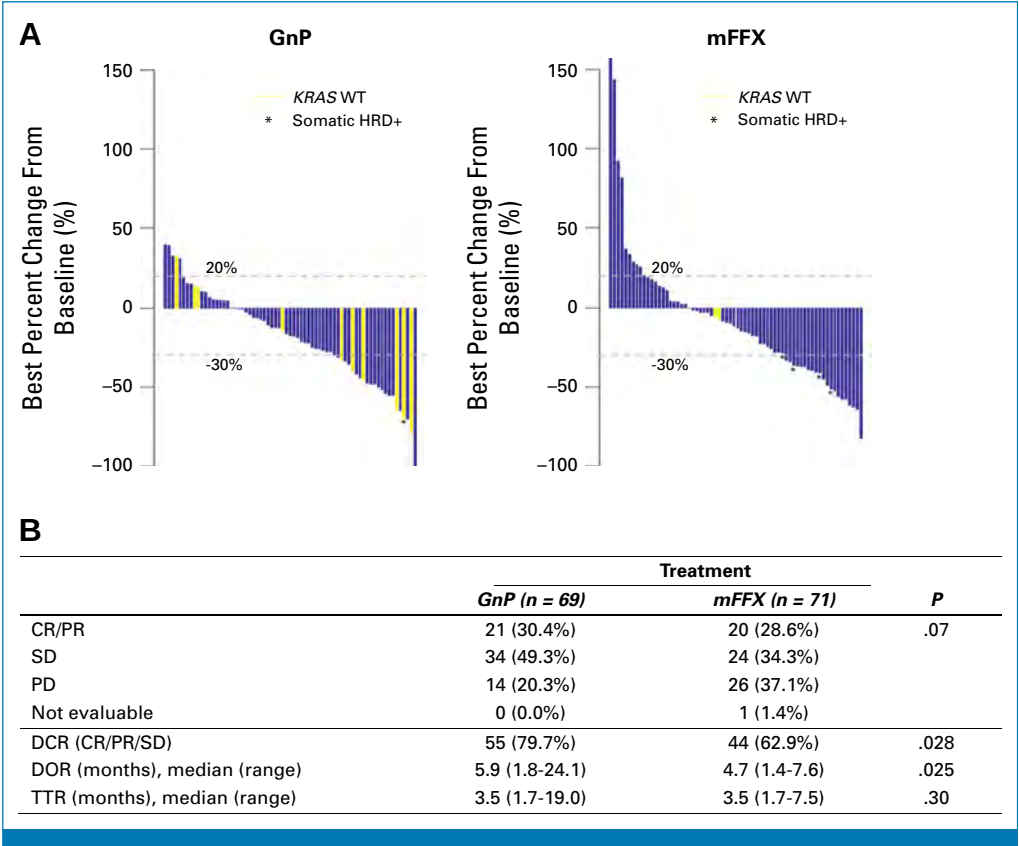


FIG 3. Response by chemotherapy. (A) Bar plot of best tumor change on first-line chemotherapy by RECIST 1.1 measurements. (B) Table comparing RECIST 1.1 for first-line response in PP population. CR, complete response; DCR, disease control rate; DOR, duration of response; FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; GnP, gemcitabine/nab-paclitaxel; HRD, homologous recombination deficiency; mFFX, modified FOLFIRINOX; PD, progressive disease; PP, per-protocol; PR, partial response; SD, stable disease; TTR, time to response; WT, wildtype.

embolism, and cerebellar stroke. The SAEs requiring admission on GnP included two for severe fatigue, and one each of nausea, cellulitis, and acute renal failure. One patient in 140 had abdominal pain requiring overnight observation from the percutaneous research biopsy (0.6%).

Outcomes by RNA Subgroup

A total of 74% (103/140) of the PP cohort could be classified into basal-like 26% (27/103) and classical 74% (76/103), with inadequate biopsy sample in the remaining. Median PFS of the basal-like group was 4.0 months versus 5.7 months in the classical group (HR, 1.19 [95% CI, 0.76 to 1.87]; $P = .44$; Fig 4A), while OS was 8.6 months for basal-like versus 10.0 months for classical (HR, 1.24 [95% CI, 0.76 to 2.04]; $P = .39$; Fig 4B). We further assessed whether RNA subtype is a predictive biomarker associated with chemotherapy benefit. Median PFS was similar for classical cases treated with mFFX versus GnP (6.3 versus 5.4 months; HR, 1.26 [95% CI, 0.77 to 2.07]; $P = .36$) but a trend for worse PFS on mFFX for basal-like cases at 3.0 months versus 5.5 months with GnP (HR, 1.76 [95% CI, 0.77 to 4.02]; $P = .17$; Fig 5A and Appendix Table A2). Median OS was worse on mFFX compared to GnP

for the classical subtype (9.7 v 13.9 months; HR, 1.80 [95% CI, 1.0 to 3.23], $P = .047$), while there was a numerically shorter median OS in the basal-like subtype for mFFX over GnP (7.5 v 8.9 months; HR, 1.14 [95% CI, 0.49 to 2.66]; $P = .75$; Fig 5B). Patients with basal-like tumors treated with GnP versus mFFX also showed numerically improved ORR (45% v 19%, $P = .20$) and DOR (5.9 v 4.8 months, $P = .55$). Patients with classical tumors treated with GnP versus mFFX had ORR of 31% v 33% ($P = .55$) and DOR of 6.7 v 4.6 months ($P = .01$).

Subsequent Line Therapy and MTB-Guided Treatments

Of 140 patients, 75 (54%) were able to start second-line therapy. More patients from the GnP arm moved to second-line than from mFFX (61% vs 55%, respectively; $P = .48$). The postprogression time-to-event patterns between two arms show no significant difference in OS between the two arms, although there is a trend for better OS for GnP group compared with mFFX (Appendix Fig A4).

RNA subtype was available in 52 second-line patients, showing classical in 38 (73%) and basal-like in 14 (27%). Of second-line treated patients, 42 (56%) received a

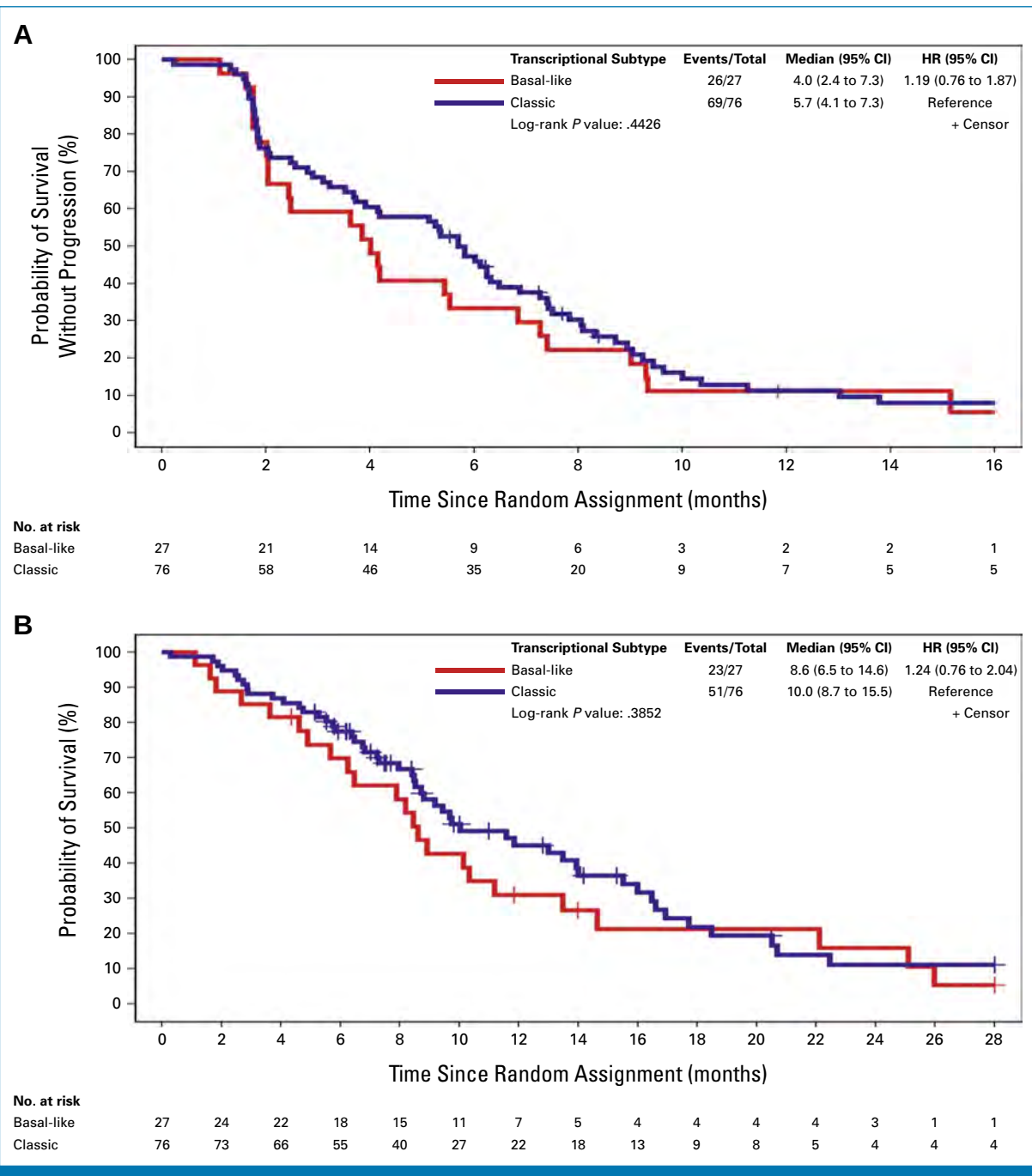


FIG 4. Association of PFS/OS with transcriptional subtype. Association of (A) PFS and (B) OS with transcriptional subtype in the 103 patients with subtype data available. HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

routine chemotherapy option and 33 (44%) patients received a correlative-guided therapy on the basis of MTB recommendations.

Specifically, WGS data informed decisions for 18 patients (55%), RNA analysis for five (15%), and PDO drug screening for 10 (30%). Patients in this trial had very limited access to KRAS inhibitor trials (1.4%), resulting in our focus on other rare actionable targets. This included BRAF inhibition, human epidermal growth factor receptor 2-directed therapy,

immune checkpoint inhibition for microsatellite instability-high and high tumor mutational burden, and drugs targeting PRMT5 or MAT2A for biallelic *MTAP* deletion. There were 12 patients identified as *KRAS* WT, a subgroup historically associated with better prognosis. Of these, nine received second-line therapy including six correlative-driven therapies guided by MTB recommendations (Table 2). Median time on second-line treatment was 2.2 months for correlative-guided and 1.9 months for routine choices. The median OS from start of second-line treatment was 5.4

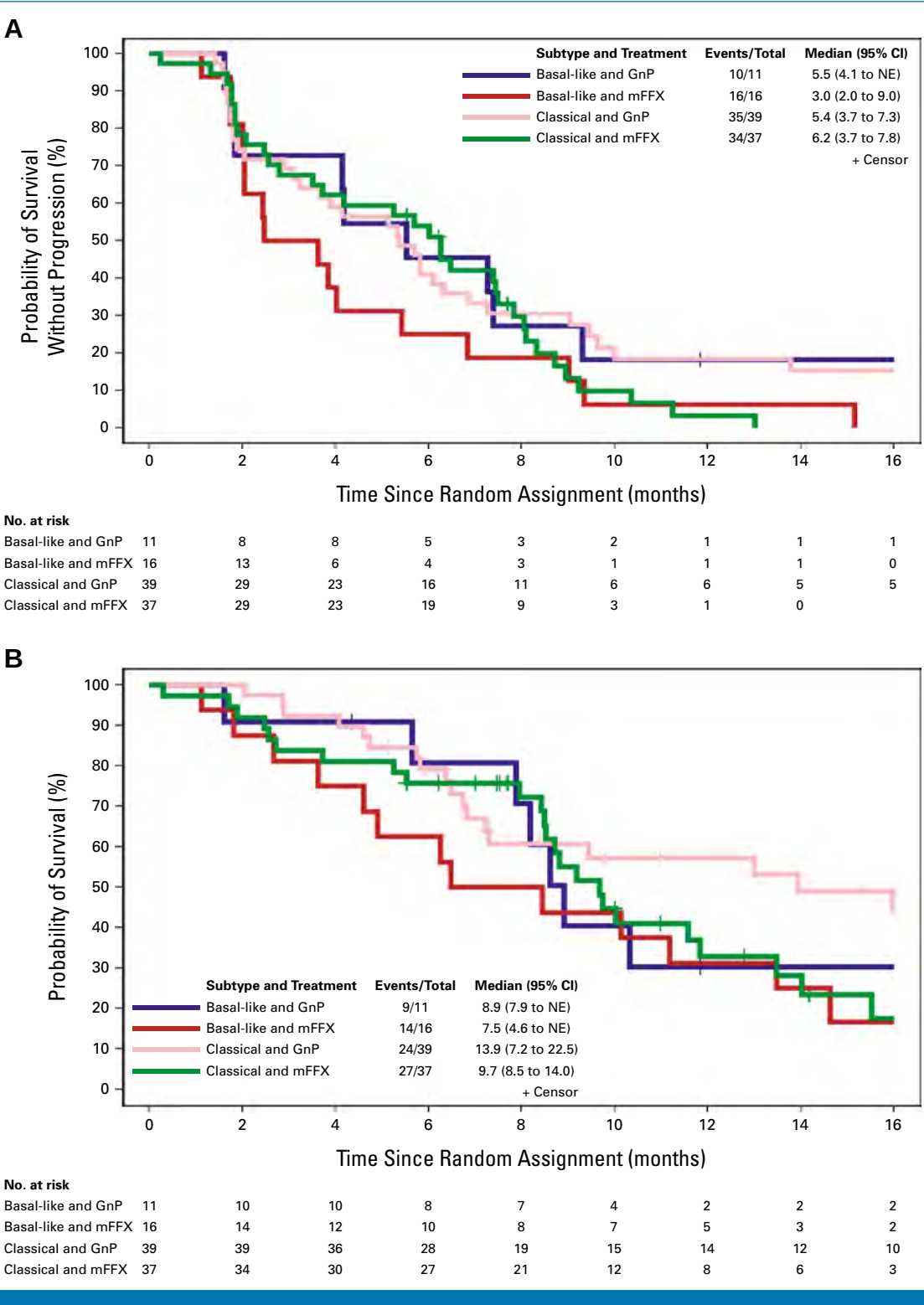


FIG 5. PFS and OS by transcriptional subgroup and treatment arm. Association of (A) PFS and (B) OS with transcriptional subtype basal-like or classical randomized to GnP or mFFX of the 103 patients with subtype data available. FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; GnP, gemcitabine/nab-paclitaxel; mFFX, modified FOLFIRINOX; NE, not evaluable; OS, overall survival; PFS, progression-free survival.

TABLE 2. Second-Line Correlative-Driven Therapies

Category	Aberration/Signature	Patients, No. (33)	Treatment Choice
Genomic aberrations (18)	<i>ERBB2</i> mutation/amplification (1 <i>KRAS</i> WT)	n = 2	T-DXd/FOLFOX + trastuzumab
	<i>BRAF</i> mutation/fusion (all <i>KRAS</i> WT)	n = 5	<i>BRAF</i> inhibitor/Mek inhibitor combination/monotherapy
	Somatic <i>BRCA-2</i> /HRD	n = 2	Gemcitabine/cisplatin
	Tandem duplicator phenotype	n = 2	mFFX
	High TMB	n = 1	Immunotherapy-based clinical trial
	Somatic MSI-H	n = 3	Pembrolizumab/nivolumab
	<i>KRAS</i> mutation	n = 2	<i>KRAS</i> inhibitor trial
	<i>MTAP</i> deletion	n = 1	PRMT5 inhibitor clinical trial
RNA signatures (5)	<i>hENT</i> high	n = 3	GnP
	Basal-like	n = 2	GnP
PDO sensitivities (10)	Chemo-specific sensitivity	n = 7	3 = gemcitabine-based 3 = platinum-based 1 = 5-FU-based
	EGFR-pathway sensitivity	n = 3	EGFR inhibitor-based agents

Abbreviations: FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; FU, 5-fluorouracil; GnP, gemcitabine/nab-paclitaxel; mFFX, modified FOLFIRINOX; *hENT*, human equilibrative nucleoside transporter¹²; HRD, homologous recombination deficiency; MSI-H, microsatellite instability-high; *MTAP*, methylthioadenosine phosphorylase; PDO, patient-derived organoid, PRMT5, protein arginine methyltransferase 5; TDXD, trastuzumab deruxtecan, TDP, tandem duplicator phenotype¹³; TMB, tumor mutational burden; WT, wildtype.

versus 4.4 months, respectively ($P = .46$). Of the 16 patients with basal-like tumors randomly assigned to mFFX in the first-line setting, 66% (6/9) showed a longer time on treatment with second-line gemcitabine-based therapy than first-line therapy, further demonstrating an impact of gemcitabine-based therapies to improve outcomes among the basal-like tumor population (Appendix Fig A5).

Outcomes by GATA6 Expression

A secondary objective of this study was to analyze *GATA6* as a potential biomarker of response to mFFX or GnP by evaluating the PFS and OS in each treatment arm according to *GATA6* ISH assay as a surrogate biomarker for classical signature. *GATA6* high by ISH correlates strongly with the classical subtype (correlation coefficient = 0.34, $P = .001$). In the PP analysis, 110/140 (79%) patients had *GATA6* expression available by ISH. There was a nonsignificant trend toward improved PFS in high expressers (5.7 months) versus low expressers (4.0 months; HR, 0.76 [95% CI, 0.48 to 1.19]; $P = .23$; Appendix Fig A6). However, there was no significant association of chemotherapy response or PFS with *GATA6* ISH (Appendix Figs A7A and A7B).

CA 19-9 as an Early Indicator of Chemotherapy Response

Of the 140 patients in the PP population, 29 (20%) were nonexpressors at enrollment (no difference by subtype). Of 95 patients (85%) with CA 19-9 data available at baseline and 4 weeks, a 20% decrease in CA19-9 was associated with better PFS (6.9 [5.7-8.3] months versus 3.7 [2.8-5.0] months, P value .0419). A > 20% increase in CA19-9 at

4 weeks was associated with inferior PFS (6.7 [5.3-7.7] months versus 3.1 [2.1-3.9] months, $P < .0001$; Figs 6A and 6B). However, 10 of 44 patients with a >20% increase in CA19-9 at 4 weeks, from a baseline CA-19-9 with median of 1,259 (range, 224-22,573), went on to have a radiologic PR or SD for >4 months. Therefore, a >20% increase in CA19-9 at 4 weeks should not be used in isolation to prompt a change in therapy. An intermediate change in CA19-9 (0%-19.9% increase or decrease at 4 weeks) had no significant change on PFS (data not shown).

DISCUSSION

To our knowledge, PASS-01 is the first randomized trial in Western countries comparing mFFX with GnP. Although PFS favored GnP at the planned 0.3 significance threshold and OS was also significantly better (10.3 v 8.7 months in those receiving chemotherapy, $P = .021$), the differences are small and outcomes remain poor with either treatment. Anticipating these limitations, PASS-01 integrated extensive correlatives and MTB review to inform later-line therapies. We demonstrated the feasibility of coordinating biospecimen collection and molecular analyses across a multicenter study. Initial translational findings highlight the worst outcomes in basal-like PDAC, although PFS, ORR, DOR, and SAEs favored GnP. OS may have been confounded by second-line treatment. Only 54% of patients were able to receive second-line therapies, and despite 44% being guided by correlatives, the benefit was minimal. Overall, PASS-01 confirms the disappointing outcomes with combination chemotherapies for metastatic PDAC, while providing important data to guide first-line therapy selection. It also demonstrated that upfront genomic profiling is

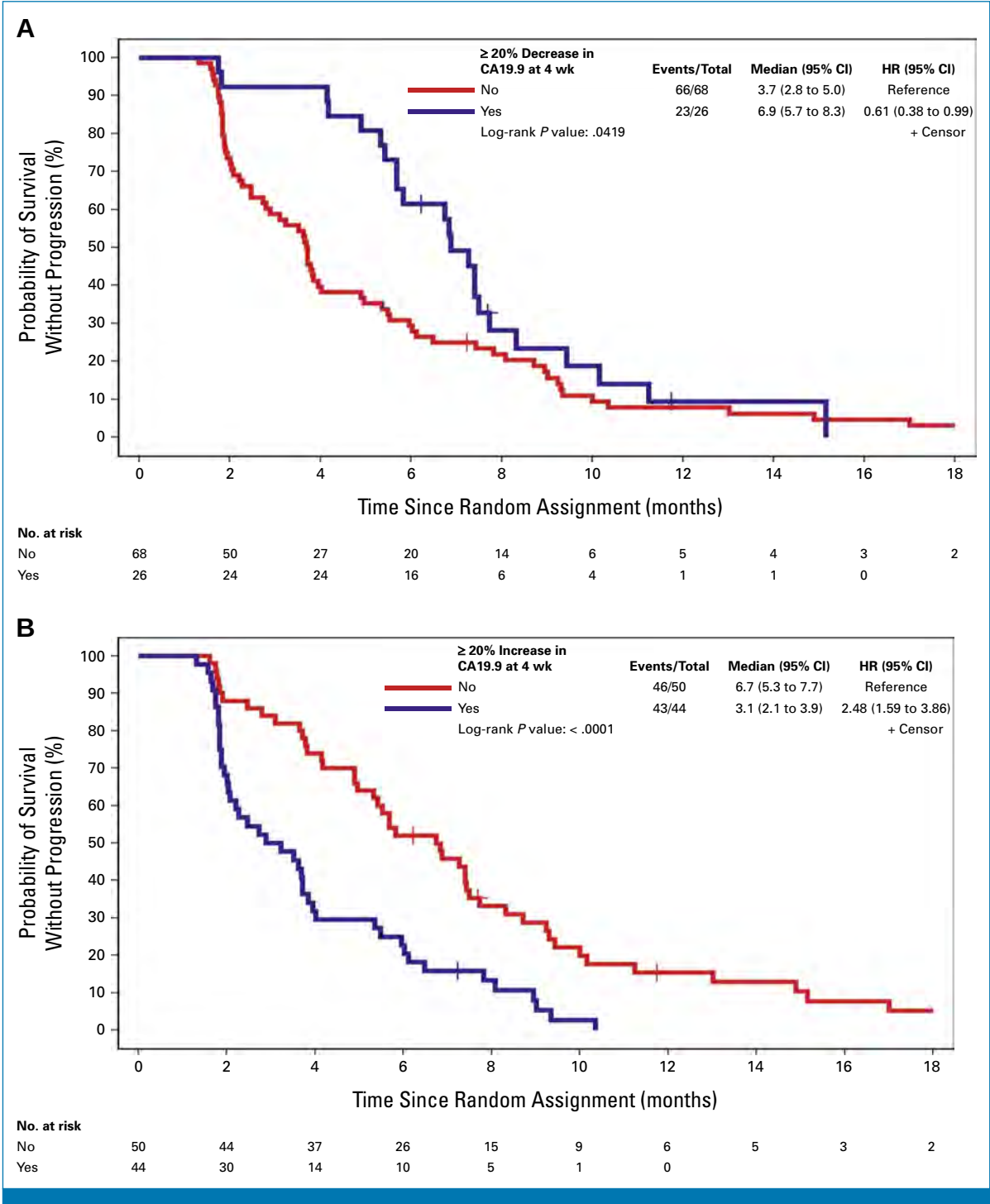


FIG 6. PFS by CA-19-9 threshold. CA 19-9 changes from baseline to 4 weeks and progression-free survival. (A) Patients with a >20 decrease in CA 19-9 had a significantly longer PFS (6.9 months [95% CI, 5.7 to 8.3]) compared with those without this decrease (3.7 months [95% CI, 2.8 to 5.0]; *P* = .0419). (B) Conversely, patients with a >20 increase in CA 19-9 had significantly shorter PFS (3.1 months [95% CI, 2.1 to 3.9]) compared with those without this increase (6.7 months [95% CI, 5.3 to 7.7]; *P* < .0001). HR, hazard ratio; PFS, progression-free survival.

feasible and supports prioritizing precision therapy in the first-line setting.

First-line combination chemotherapy has improved OS for patients with metastatic pancreatic cancer, but survival

remains modest at under 1 year.^{3,6} A systematic review and a phase III meta-analysis show little difference in efficacy outcomes between three regimens, slightly favoring mFFX or NALIRIFOX over GnP.^{4,5} A direct mFFX versus NALIRIFOX comparison has not been conducted, and NALIRIFOX was

unavailable during PASS-01 study design. The Japanese GENERATE trial, not included in these reviews, favored GnP over mFFX or S-IROX, with median OS of 17, 14, and 13.6 months, respectively.¹⁴ PASS-01 also favors GnP over mFFX by PFS, OS, response duration, and less chemo-related SAEs. However, these differences are modest, but are practice-informing, and help clinicians guide first-line treatment decisions.

PASS-01's patient population differed from previous trials in ways that may have influenced the results. First, patients with known or suspected germline variants *BRCA1/2* or *PALB2* mutations—recognized biomarkers for better platinum-based chemotherapy—were excluded (approximately 10% of metastatic PDAC cases). A subgroup analysis of *BRCA1/2* or *PALB2* mutations from NAPOLI-3 trial could be informative. Next, to ensure all patients would be chemo-naïve, for PDO pharmacotyping, those with recurrent disease after resection were excluded (generally 7%–10% of first-line trials). Bulky metastases were needed for biopsies and so patients with low volume or lung-only metastasis, known to have better outcomes, were not accrued. All these criteria are potentially selecting for more aggressive presenting disease and higher risk of early symptomatic decline. PASS-01 also enrolled a more diverse population (64% White v 83%–87% historically^{2,6}), better reflecting North American patients, although the impact of race on outcome remains unclear. Despite these differences, the GnP arm performed as expected, with a median OS close to 10 months, and particularly well in the classical tumor subgroup with a median OS of 14 months. By contrast, the mFFX arm underperformed relative to historical data with a median OS of 8.7 months.

Second-line efficacy was disappointing, despite efforts to use correlative driven selections where available. Second-line therapy was investigator-determined with no protocolized PS criteria, likely contributing to poorer outcomes because of rapid clinical decline. Nevertheless, these data represent real-world experience and align with other trials attempting personalized treatment in PDAC.¹⁵

Transcriptional subtypes emerge as an important prognostic factor in this randomized data set, with basal-like cases showing numerically worse outcomes, particularly with mFFX. These results build on previous nonrandomized data,¹⁰ highlighting the need for assessment of transcriptional subtype early in treatment selection rather than making a

decision agnostic of subtype. Emerging chemotherapy-prediction signatures could be compared blindly on PASS-01 data to build validation and consensus. This has implication for future trials, where basal-like tumors could be prioritized for novel first-line approaches using a GnP backbone for potentially better efficacy with less toxicity (eg, ClinicalTrials.gov identifier: [NCT06483555](https://clinicaltrials.gov/ct2/show/study?term=NCT06483555)). As RAS inhibitors enter the clinic, understanding the subtype specific on sensitivity may inform combination strategies.^{16,17} Our findings on early dynamic changes of CA-19-9 build on previous data¹⁸ and demonstrate very early CA19-9 changes is a strong biomarker and, perhaps if when combined with another marker such as ctDNA, could support early switch strategies in trials, potentially before a clear radiologic or clinical decline.

The main limitation of this trial is the relatively small phase II design, leading to underpowered end points, especially the predictive and exploratory analyses. The more relaxed alpha allowed a better chance of detecting an efficacy signal in either arm and in a more select population than previously tested, but with a higher risk of a false positive. This was an acceptable design recognizing that a larger trial comparing these well-established regimens would have been very difficult to execute. Chance imbalances in patient characteristics between arms may have affected outcomes, although that is not supported by the multivariable analysis, and small differences do not change our conclusions. This smaller study permitted a rich biomarker data set with high rates of biospecimen collection to guide future research. Underpowered subgroups could be combined with other known data sets to refine findings further. The future clinical utility of GATA-6 as a biomarker is likely to be complemented by implementation of a multiplex immunofluorescence pipeline with multiple protein expressions¹⁹ or commercial signatures.

PASS-01 paves the way for upfront profiling and biomarker-driven treatment selection. Advances in profiling technologies now enable rapid genomic stratification that would allow for integral biomarker selection trials. As we enter the era of RAS inhibitors, and other promising strategies expand treatment options, it is important to remember only approximately 50% of patients receive second-line therapy and outcomes remain poor, even with targeted treatments. Optimizing first-line precision approaches is critical for patients with PDAC.

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CLINICAL TRIAL INFORMATION

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Tong H, Fan Z, Liu B, et al: The benefits of modified FOLFIRINOX for advanced pancreatic cancer and its induced adverse events: A systematic review and meta-analysis. *Sci Rep* 8:8666, 2018
2. Von Hoff DD, Ervin T, Arena FP, et al: Increased survival in pancreatic cancer with nab-Paclitaxel plus gemcitabine. *N Engl J Med* 369(18):1691-1703, 2013
3. Conroy T, Desseigne F, Ychou M, et al: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 364(19):1817-1825, 2011
4. Nichetti F, Rota S, Ambrosini P, et al: NALIRIFOX, FOLFIRINOX, and gemcitabine with nab-paclitaxel as first-line chemotherapy for metastatic pancreatic cancer: A systematic review and meta-analysis. *JAMA Netw Open* 7:e2350756, 2024
5. Merza N, Farooqui SK, Dar SH, et al: Folfirinox vs. gemcitabine + nab-paclitaxel as the first-line treatment for pancreatic cancer: A systematic review and meta-analysis. *World J Oncol* 14(5): 325-339, 2023
6. Wainberg ZA, Melisi D, Macarulla T, et al: NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-naïve patients with metastatic pancreatic ductal adenocarcinoma (NAPOLI 3): A randomised, open-label, phase 3 trial. *Lancet (London, England)* 402:1272-1281, 2023

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A data sharing statement provided by the authors is available with this article at DOI <https://doi.org/10.1200/JCO-25-00436>.

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7. Rebelatto TF, Falavigna M, Pozzari M, et al: Should platinum-based chemotherapy be preferred for germline BRCA 1 and 2-mutated pancreatic ductal adenocarcinoma (PDAC) patients? A systematic review and meta-analysis. *Cancer Treat Rev* 80:101895, 2019
8. Moffitt RA, Marayati R, Flate EL, et al: Virtual microdissection identifies distinct tumor- and stroma-specific subtypes of pancreatic ductal adenocarcinoma. *Nat Genet* 47:1168-1178, 2015
9. Aung KL, Fischer SE, Denroche RE, et al: Genomics-driven precision medicine for advanced pancreatic cancer: Early results from the COMPASS trial. *Clin Cancer Res* 24:1344-1354, 2018
10. O'Kane GM, Grünwald BT, Jang GH, et al: GATA6 expression distinguishes classical and basal-like subtypes in advanced pancreatic cancer. *Clin Cancer Res* 26:4901-4910, 2020
11. Tiriack H, Belleau P, Engle DD, et al: Organoid profiling identifies common responders to chemotherapy in pancreatic cancer. *Cancer Discov* 8:1112-1129, 2018
12. Perera S, Jang GH, Wang Y, et al: hENT1 expression predicts response to gemcitabine and Nab-Paclitaxel in advanced pancreatic ductal adenocarcinoma. *Clin Cancer Res* 28:5115-5120, 2022
13. Farooq AR, Zhang AX, Chan-Seng-Yue M, et al: The tandem duplicator phenotype may be a novel targetable subgroup in pancreatic cancer. *NPJ Precis Oncol* 9:100, 2025
14. Ohba A: Nab-paclitaxel plus gemcitabine versus modified FOLFIRINOX or S-IROX in metastatic or recurrent pancreatic cancer (JCOG1611, GENERATE): A multicenter, randomized, open-label, three-arm, phase 2/3 trial. 2023
15. Sarno F, Tenorio J, Perea S, et al: A phase III randomized trial of integrated genomics and avatar models for personalized treatment of pancreatic cancer: The AVATAR trial. *Clin Cancer Res* 31:278-287, 2025
16. Singhal A, Styers HC, Rub J, et al: A classical epithelial state drives acute resistance to KRAS inhibition in pancreatic cancer. *Cancer Discov* 14:2122-2134, 2024
17. Dilly J, Hoffman MT, Abbassi L, et al: Mechanisms of resistance to oncogenic KRAS inhibition in pancreatic cancer. *Cancer Discov* 14:2135-2161, 2024
18. Robert M, Jarlier M, Gourgou S, et al: Retrospective analysis of CA19-9 decrease in patients with metastatic pancreatic carcinoma treated with FOLFIRINOX or gemcitabine in a randomized phase III study (ACCORD11/PRODIGE4). *Oncology* 93:367-376, 2017
19. Williams HL, Dias Costa A, Zhang J, et al: Spatially resolved single-cell assessment of pancreatic cancer expression subtypes reveals co-expressor phenotypes and extensive intratumoral heterogeneity. *Cancer Res* 83:441-455, 2023

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

PASS-01: Randomized Phase II Trial of Modified FOLFIRINOX Versus Gemcitabine/Nab-Paclitaxel and Molecular Correlatives for Previously Untreated Metastatic Pancreatic Cancer

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Patents, Royalties, Other Intellectual Property: We have filed a provisional use patent for 5B1 to use to treat pancreatitis. with MabVax, which was acquired by BionTech, anti-CA199 for pancreatitis (pending)

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Patents, Royalties, Other Intellectual Property: I developed GVAX which is being tested in the clinics. It was licensed to Adoro Biotech. If it becomes commercial, I will have the potential to receive royalties. Also, I have received milestone payments yearly, I developed antigen-targeted vaccines that are being tested in the clinic. Adventris will support these studies in the future due to recent licensing

Other Relationship: Break Through Cancer

No other potential conflicts of interest were reported.

APPENDIX

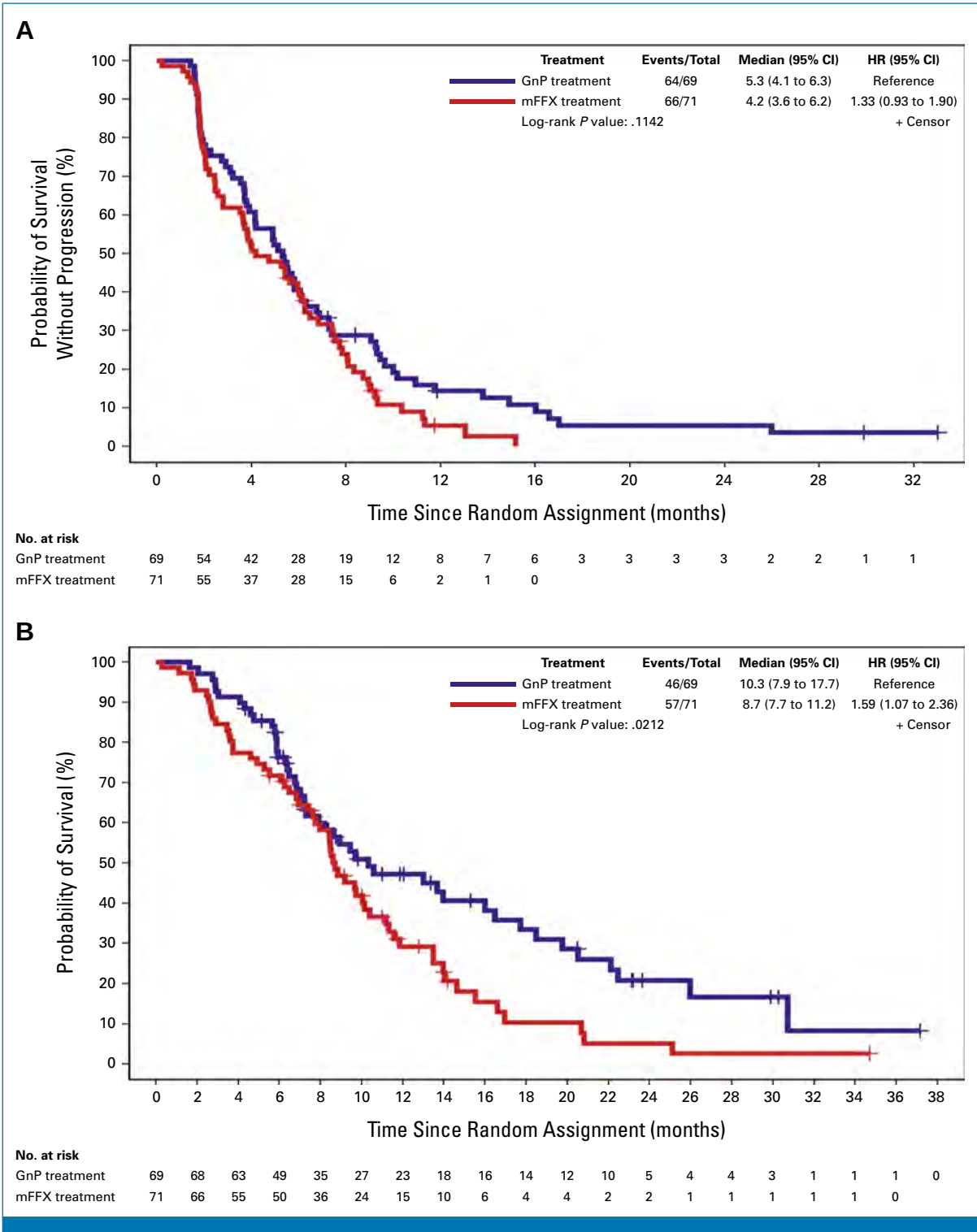


FIG A1. Comparison of (A) PFS and (B) OS between two treatment groups: mFFX and GnP treatment for PP population (140 patients). FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; GnP, gemcitabine/nab-paclitaxel; HR, hazard ratio; mFFX, modified FOLFIRINOX; OS, overall survival; PFS, progression-free survival; PP, per-protocol.

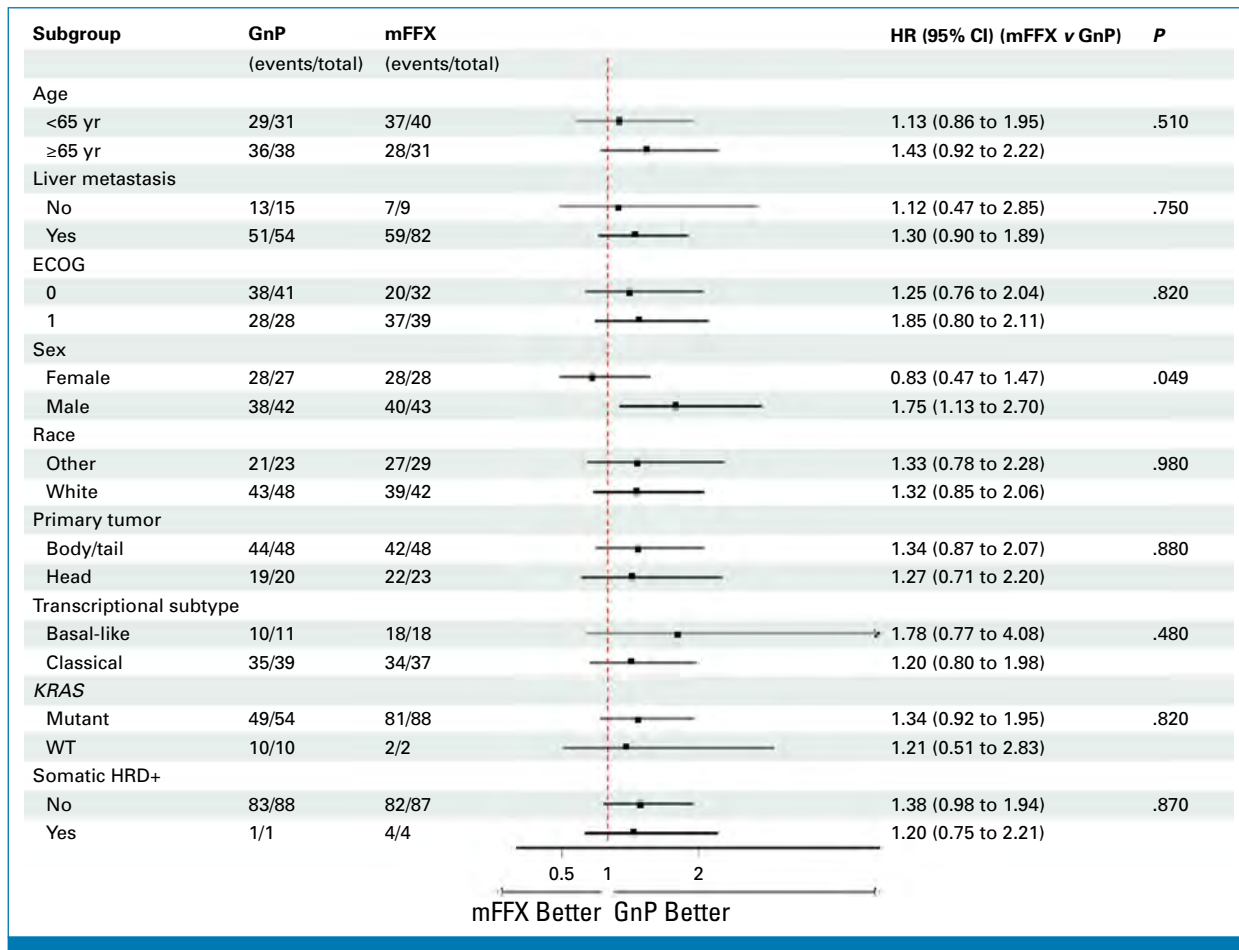


FIG A2. Subgroup analysis of PFS. ECOG, Eastern Cooperative Oncology Group; FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; GnP, gemcitabine/nab-paclitaxel; HR, hazard ratio; HRD, homologous recombination deficiency; mFFX, modified FOLFIRINOX; PFS, progression-free survival; WT, wildtype.

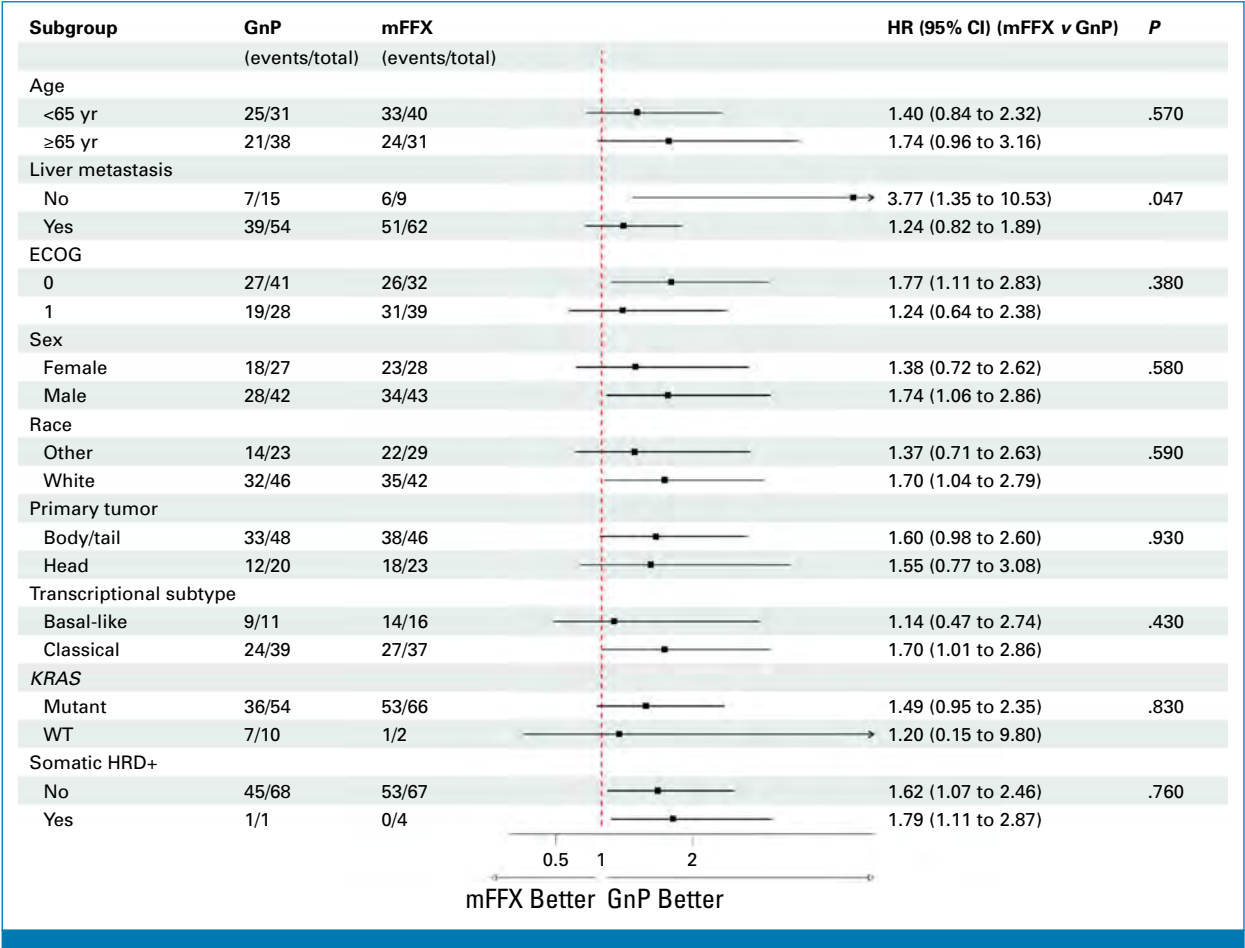


FIG A3. Subgroup analysis of OS. ECOG, Eastern Cooperative Oncology Group; FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; GnP, gemcitabine/nab-paclitaxel; HR, hazard ratio; HRD, homologous recombination deficiency; mFFX, modified FOLFIRINOX; OS, overall survival; WT, wildtype.

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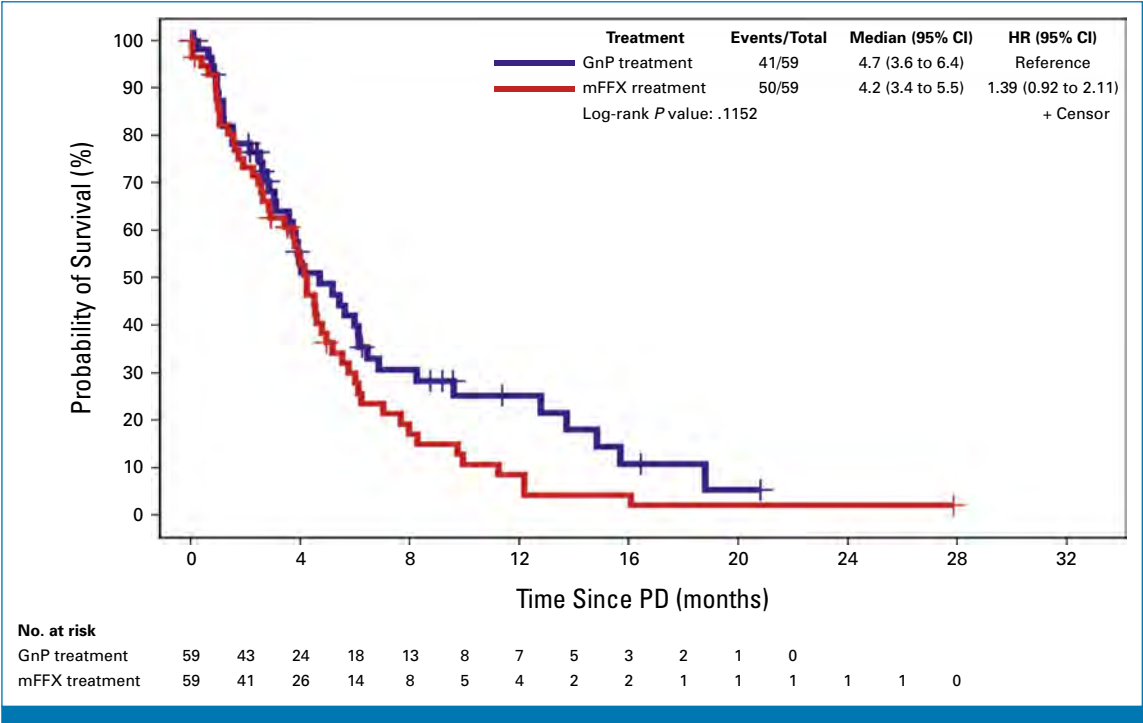


FIG A4. Subgroup analysis: comparison of post-PD OS between two treatment groups in those with PD (*n* = 118) in PP population. FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; GnP, gemcitabine/nab-paclitaxel; HR, hazard ratio; mFFX, modified FOLFIRINOX; OS, overall survival; PD, progressive disease; PP, per-protocol.

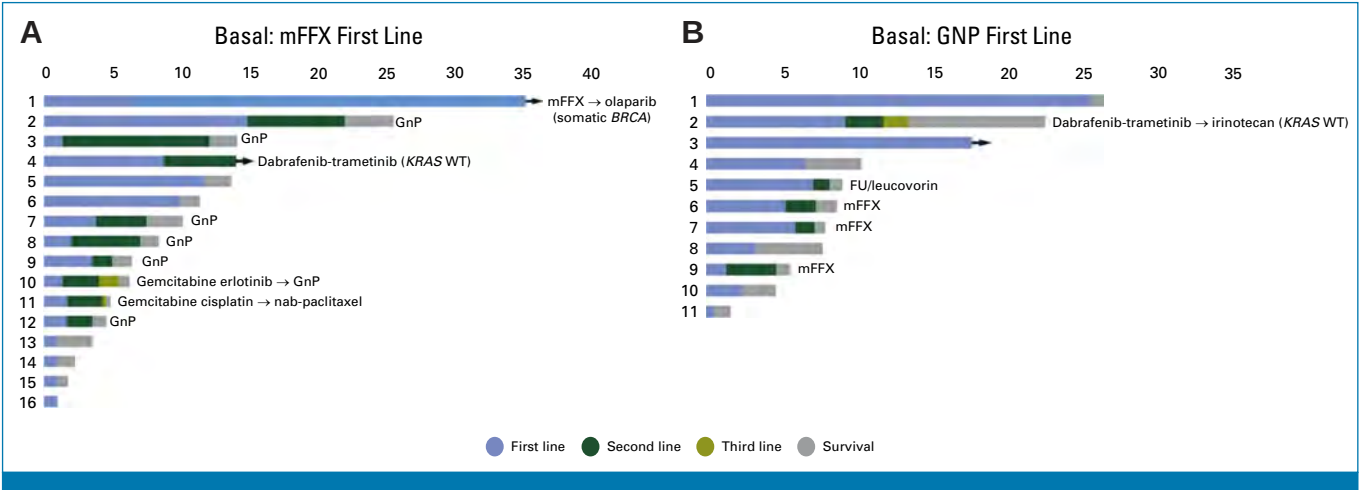


FIG A5. Swimmer plot of first-line and subsequent line treatments of basal-like subgroup patients. Each horizontal bar represents a single patient's timeline measured in months: (A) mFFX and (B) GnP. FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; FU, fluorouracil; GnP, gemcitabine/nab-paclitaxel; mFFX, modified FOLFIRINOX.

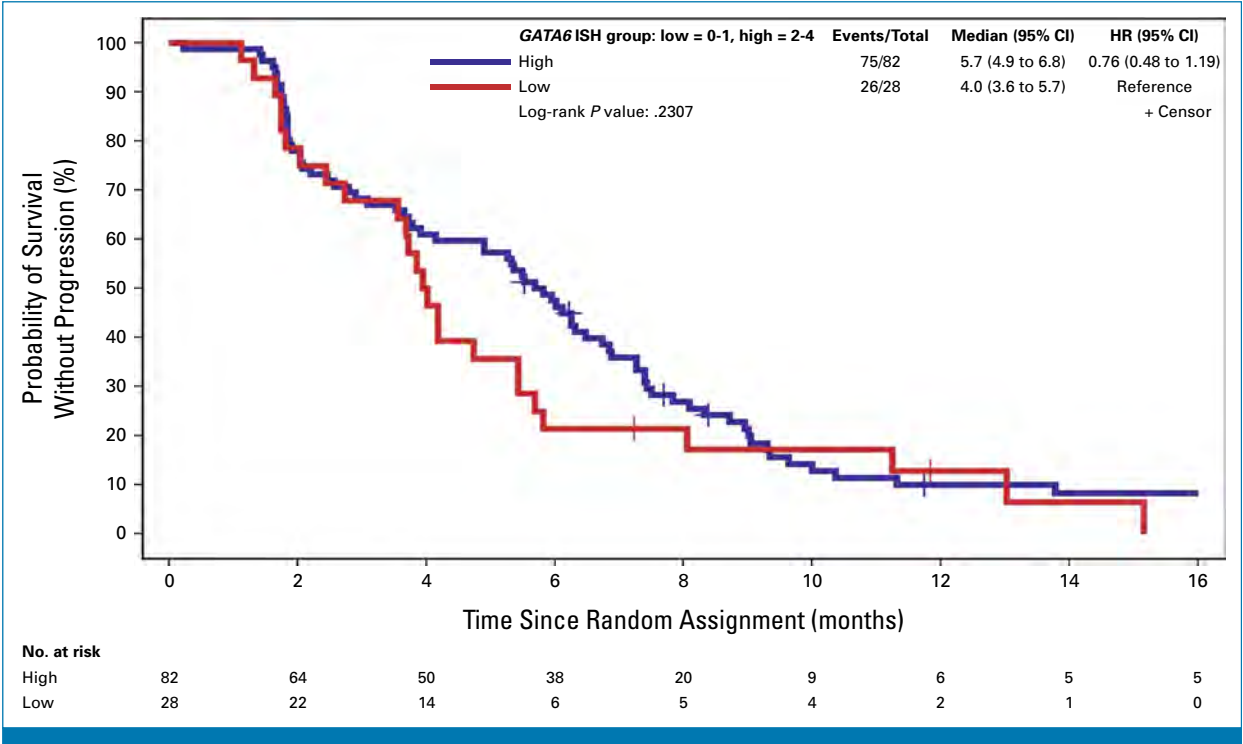


FIG A6. Comparisons of PFS between *GATA6* ISH (high v low) for all 110 patients with *GATA6* ISH information available. HR, hazard ratio; ISH, in situ hybridization; PFS, progression-free survival.

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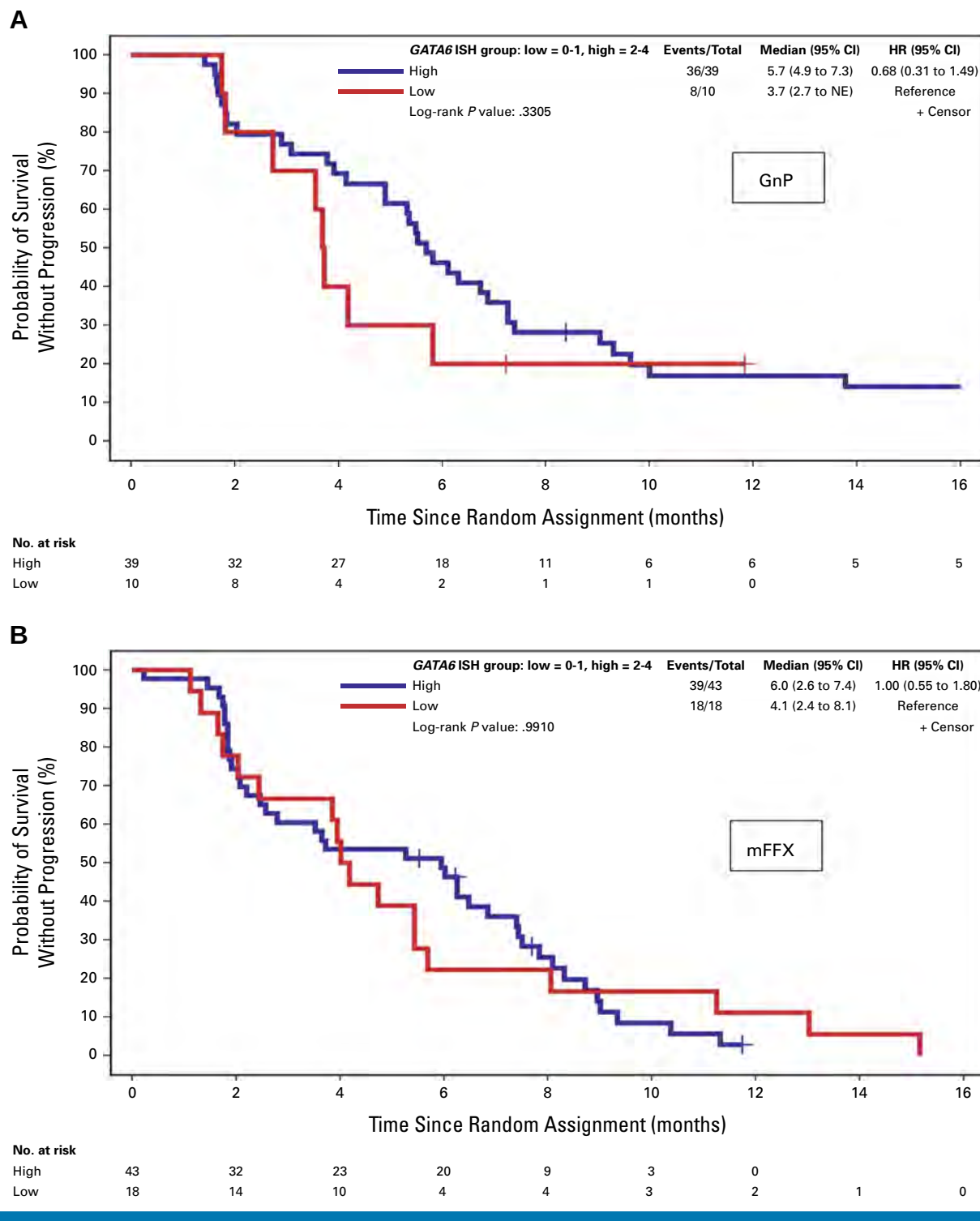


FIG A7. PFS by GATA6 ISH high versus low stratified by treatment arm. (A) Comparison of PFS between GATA6 ISH groups: high versus low in GnP treatment arm. (B) Comparison of PFS between GATA6 ISH groups: high versus low in mFFX treatment arm. FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; GnP, gemcitabine/nab-paclitaxel; HR, hazard ratio; ISH, in situ hybridization; mFFX, modified FOLFIRINOX; NE, not evaluable; PFS, progression-free survival.

TABLE A1. Association of Treatment With End Points

End Point	Treatment	Model I		Model II	
		HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
PFS	mFFX v GnP	1.33 (0.93 to 1.90)	.12	1.27 (0.87 to 1.85)	.21
OS	mFFX v GnP	1.59 (1.07 to 2.36)	.02	1.25 (0.81 to 1.93)	.31

NOTE: PP analysis: Model I: no adjustment. Model II: adjusted for potential confounders ECOG PS, liver metastasis, and *KRAS* WT.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; GnP, gemcitabine/nab-paclitaxel; HR, hazard ratio; mFFX, modified FOLFIRINOX; OS, overall survival; PFS, progression-free survival; PP, per-protocol; WT, wildtype.

TABLE A2. Summary of PFS and OS by Transcriptional Subtype and Treatment Arm

Transcriptional Subtype	Treatment	PFS			OS		
		mPFS (95% CI)	HR (95% CI)	<i>P</i>	mOS (95% CI)	HR (95% CI)	<i>P</i>
Classical	mFFX	6.3 (3.7 to 7.8)	1.26 (0.77 to 2.07)	.36	9.7 (8.5 to 14.0)	1.80 (1.0 to 3.23)	.047
	GnP	5.4 (3.7 to 7.3)	Ref		13.9 (7.2 to 22.5)	Ref	
Basal-like	mFFX	3.0 (2.0 to 9.0)	1.76 (0.77 to 4.02)	.17	7.5 (4.6 to NE)	1.14 (0.49 to 2.66)	.75
	GnP	5.5 (4.1 to NE)	Ref		8.9 (7.9 to NE)	Ref	

NOTE. The results were based on the KM analysis stratified by subtype.

Abbreviations: FOLFIRINOX, folinic acid/leucovorin, fluorouracil, irinotecan, oxaliplatin; GnP, gemcitabine/nab-paclitaxel; HR, hazard ratio; mFFX, modified FOLFIRINOX; mOS, median of OS (months); mPFS, median of PFS (months); NE, not evaluable; OS, overall survival; *P*, *P* value on the basis of log-rank test; PFS, progression-free survival; Ref, reference.

Appendix KOBAYASHI01

common being decreased neutrophil count. Patients with PD-L1 TPS $\geq 1\%$ showed a higher ORR (66.7% vs. 25.0%), as well as longer median PFS (6.3 vs. 5.3 months) and median OS (18.8 vs. 9.9 months). Fibrosis-associated signatures (such as ECM-myCAF and IL-ICAF) and pSMAD2/3 level were associated with anti-tumor activity.

Conclusions: SHR-1701 combined with AG showed positive antitumor activity and controllable safety in advanced pancreatic cancer.

Clinical trial identification: NCT04624217.

Legal entity responsible for the study: The authors.

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Disclosure: All authors have declared no conflicts of interest.

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1527P GnP vs mFOLFIRINOX or S-IROX in metastatic pancreatic cancer: 1-year follow-up updated data from the GENERATE (JCOG1611)

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Background: We previously reported that the superiority of modified FOLFIRINOX (mFOLFIRINOX) and S-IROX (S-1, irinotecan, and oxaliplatin) compared with Gemcitabine (G) plus nab-paclitaxel (nP) (GnP) were not demonstrated as first-line treatment for metastatic pancreatic cancer (MPC). We report the final follow-up updated data.

Methods: This randomized, open-label, phase 2/3 trial was done in 45 Japanese centers. Eligible patients (pts) were aged 20–75 years and had an ECOG PS of 0–1 with pathologically confirmed metastatic or recurrent pancreatic cancer. Pts were randomly allocated (1:1:1) to receive GnP (G 1,000 mg/m² and nP 125 mg/m² on days 1, 8, 15, every 4 weeks), mFOLFIRINOX (oxaliplatin 85 mg/m², irinotecan 150 mg/m², and l-leucovorin 200 mg/m² on day 1, and 5-FU 2,400 mg/m² on days 1–3, every 2 weeks), or S-IROX (oxaliplatin 85 mg/m² and irinotecan 150 mg/m² on day 1, and S-1 80 mg/m²/day on days 1–7, every 2 weeks). The primary endpoint was overall survival (OS).

Results: From Apr 2019 to Mar 2023, 527 pts were included and analyzed for the final analysis. The median OS was 15.3 mo in the GnP arm, 12.5 mo in the mFOLFIRINOX arm (HR 1.27, 95% CI 1.01–1.61), and 13.2 mo in the S-IROX arm (HR 1.23, 95% CI 0.98–1.56). The median progression-free survival was 6.5 mo in the GnP arm, 5.9 mo in the mFOLFIRINOX arm (HR 1.06, 95% CI 0.86–1.32), and 6.0 mo in the S-IROX arm (HR 0.96, 95% CI 0.77–1.20). Subsequent anti-cancer therapy was administered in 85.8% of GnP arm, 86.9% of mFOLFIRINOX arm, and 87.5% of S-IROX arm. Nal-IRI-based regimens were administered as the 2nd-line setting in 22.2% of the GnP arm, 1.1% of the mFOLFIRINOX arm, and 0.6% of the S-IROX arm. In the BRCA mutated pts, OS was longer than that in wild type pts in all 3 arms (GnP 25.9 mo, mFOLFIRINOX 18.4 mo, S-IROX 33.2 mo). Grade 3 or higher anorexia was more frequent in the mFOLFIRINOX (22.8%) and S-IROX (27.6%) arm than in the GnP arm (5.2%).

Conclusions: In the final analysis as well as in the interim analysis, GnP is recommended as the first-line treatment for pts with MPC compared to mFOLFIRINOX or S-IROX.

Clinical trial identification: jRCT031190009.

Legal entity responsible for the study: Japan Clinical Oncology Group (JCOG), Hepatobiliary and Pancreatic Oncology Group (HBPOG).

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1528P TCOG T5221 trial: A phase II randomized study of gemcitabine and nab-paclitaxel in combination with S- 1/LV (GASL) or oxaliplatin (GAP) as first-line treatment for metastatic pancreatic cancer

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Background: Gemcitabine plus nab-paclitaxel (GnP), given weekly for consecutive 3 weeks every 4 weeks, is one of the standard treatment for metastatic pancreatic adenocarcinoma (mPDAC); however, the objective response rate (ORR) is only 23% and the standard GnP is too toxic for Asian (71% grade 3–4 neutropenia in the Japanese study). Prior study showed biweekly GnP could reduce toxicities, which provided the opportunity to add other agents to overcome tumor heterogeneity. This study aims to assess the efficacy and safety of biweekly GnP plus either S-1/LV (GASL) or oxaliplatin (GAP).

Methods: The major inclusion criteria were histologically confirmed mPDAC with adequate organ functions. The primary endpoint was ORR. Utilizing a 'pick the winner' approach, a parallel Simon two-stage design was employed to test if ORR could achieve 41% in either arm. The study arm would proceed to the second stage if there were 6 or more responders among the first 24 patients in each arm. Both arm consisted of nab-paclitaxel 125 mg/m², gemcitabine 800 mg/m² on day 1 in a 2-week

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Appendix LI02



Original Article

Modified-FOLFIRINOX in metastatic pancreatic cancer: A prospective study in Chinese population



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ABSTRACT

FOLFIRINOX chemotherapy has shown remarkable responses in patients with metastatic pancreatic cancer (MPC), and has significantly improved prognosis. However, FOLFIRINOX is currently not frequently applied in China because of its high incidence of adverse events, and there is no recognized optimization for this therapy in Chinese population. Modification of FOLFIRINOX may be better for its acceptance in China. In this study, we evaluated the efficacy and safety of modified-FOLFIRINOX in patients with MPC. A total of 62 MPC patients were treated with modified-FOLFIRINOX (no Fluorouracil bolus, 85% Oxaliplatin and 75% Irinotecan) between April 2014 and April 2017 in our institute. 40 of them were evaluated, with a response rate of 32.5% (13/40). The frequent grade 3/4 adverse events are neutropenia (29%) and alanine aminotransferase elevation (14.5%). No treatment-related death was observed. The median overall survival and median progression-free survival are 10.3 months and 7.0 months, respectively. In conclusion, modified-FOLFIRINOX had significantly improved tolerance with similar efficacy to FOLFIRINOX. These findings may provide evidence for the use of FOLFIRINOX in Chinese patients with MPC.

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Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death worldwide [1], because of difficulty in diagnosis, early tumor metastasis and tumor resistance to current therapies [2,3]. The incidence in China was approximately 90,100 patients and the mortality was 79,400 in 2015 [4], while the 5-year overall survival (OS) rate remains around 4.1% [5]. Only 15–20% of patients are

eligible for potentially curative surgery, and the remaining patients are defined as locally advanced disease or distant metastasis [6].

Systemic chemotherapy is frequently used to treat patients with metastatic pancreatic cancer (MPC). In the past decade, gemcitabine has replaced 5-fluorouracil and been recognized as the first choice for pancreatic cancer patients, with a 1.2-months increase in median overall survival (OS) [7]. However, the response rate of gemcitabine monotherapy remains low (approximately 10%), and an improved strategy is desperately needed [7,8]. FOLFIRINOX (a combination of fluorouracil, oxaliplatin, irinotecan and leucovorin) achieved much longer median OS in locally advanced pancreatic cancer [9]. Recently, FOLFIRINOX has also been shown to acquire significant longer median OS and progression-free survival (PFS) of 11.1 and 6.4 months, respectively, in MPC as well as an increased

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response rate of 31.6% [10]. A meta-analysis, with twenty randomized controlled trials and 6264 patients, was conducted to compare the efficacy of twelve chemotherapy regimens in treating advanced or metastatic pancreatic cancer, and FOLFIRINOX was found to be the best option in terms of better objective response rate (ORR), OS, and PFS [11]. Therefore, FOLFIRINOX has been considered as the first-line chemotherapy regimen for MPC in recent years.

However, the survival gain comes at a cost. Compared to gemcitabine, FOLFIRINOX is reported with a higher rate of grade 3/4 adverse events, including neutropenia (45.7% vs. 21%), fatigue (23.6% vs. 17.8%), vomiting (14.5% vs. 8.3%), diarrhea (12.7% vs. 1.8%), and sensory neuropathy (9% vs. 0%) [10]. For this reason, FOLFIRINOX was only used in patients with very good performance status at full dose, and the tolerability still remains a main concern [12]. As a result, an increasing number of studies have aimed to improve chemotherapeutic or targeted therapy regimens to reduce toxicity without compromising efficacy (Table 1) [13–16]. Using dose attenuation, Mahaseth et al. reported a significantly reduced incidence of adverse events with a similar median OS (9.0 vs. 11.1 months compared to full dose) [14]. Similarly, Stein et al. demonstrated that reduction of irinotecan and bolus 5-fluorouracil by 25% resulted in significantly decreased neutropenia, vomiting, and fatigue, with a relatively high response rate of 35.1% [15].

Compared with Chinese population, Europeans present with physical advantages and show greater tolerance against the adverse effects of chemotherapy. FOLFIRINOX is currently not popular in China because of its safety. Currently, there is no standard regimen for FOLFIRINOX in China. The present study investigated the efficacy of the modified-FOLFIRINOX regimen in patients with MPC. As far as we know, this is the first study to evaluate FOLFIRINOX in Chinese patients with metastatic pancreatic cancer. We hope more Chinese patients can benefit from FOLFIRINOX with dose modification.

Materials and methods

Patients

This was a prospective study involving MPC patients receiving adjuvant modified-FOLFIRINOX from April 2014 to April 2017 at the Department of Hepatobiliary and Pancreatic Surgery, the Second Affiliated Hospital, Zhejiang University School of Medicine. Patients who were histologically diagnosed with pancreatic adenocarcinoma and were prescribed modified-FOLFIRINOX, with or without prior treatments, were eligible for inclusion. In all cases, MPC was diagnosed by a multidisciplinary team according to the National Comprehensive Cancer Network definitions. Exclusion criteria were: (1) Eastern Cooperative Oncology Group (ECOG) performance score higher than 1; (2) inadequate bone marrow, liver or renal functions; (3) with additional malignancies; (4) older than 75 years. Our study followed the Declaration of Helsinki, and all included patients provided written informed consent.

Table 1

The efficacy and safety of FOLFIRINOX in advanced pancreatic cancer patients.

Events	Full dose	Modified dose			
	Conroy [10]	Stein [15]	Mahaseth [14]	Rombouts [16]	Our Center
Patients, n	166	68	60	50	62
Stage, %					
Locally advanced	0	45.6	40	36	0
Metastatic	100	54.4	60	64	100
Outcomes					
OS (MPC), months	11.1	10.2	11.1	9.0	10.3
PFS (MPC), months	6.4	6.1	9.0	5.9	7.0
ORR, %	31.6	35.1	30	32	32.5
Grade 3/4 AEs, %					
Neutropenia	45.7	12.2	3	40	29
Fatigue	23.6	12.2	13	8	0
Vomiting	14.5	2.7	8	2	0
Diarrhea	12.7	16.2	13	4	0

Assessments

All patients were evaluated every four cycles of modified-FOLFIRINOX using chest high-resolution computed tomography (HRCT) scan, abdominal enhanced computed tomography (CT), and enhanced magnetic resonance imaging (MRI) of the liver. Physical examination and laboratory tests were performed every time before chemotherapy. Tumor response was categorized into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (version 1.1) [17]. Serum cancer antigen (CA) 19-9 levels were examined at the time of tumor response assessment. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). OS was defined as the duration from the beginning of chemotherapy to the date of death of any cause. PFS was defined as the duration from the beginning of chemotherapy to the date of disease progression or death. Patients without event were censored at the last follow-up date (May 1st, 2017). For patients with modified-FOLFIRINOX, information were collected at the moment of admission. While patients who had discharged were followed up every 3 months in clinic with physical examination, laboratory tests, chest HRCT, abdominal enhanced CT and enhanced MRI of the liver.

Treatment

The FOLFIRINOX regimen was modified by reducing oxaliplatin and irinotecan to 85% and 75% of the full dose, respectively, and omitting the fluorouracil intravenous bolus. The detailed treatment plan is as follows: a 2-h intravenous infusion of oxaliplatin (68 mg/m²), followed by another 2-h intravenous infusion of leucovorin (400 mg/m²), concomitantly with an additional 1.5-h intravenous infusion of irinotecan (135 mg/m²), and a subsequent intravenous infusion of fluorouracil (2400 mg/m²) over 46 h. For all patients, anti-emetic agents (ondansetron, azasetron, and metoclopramide), omeprazole, and dexamethasone were used to enhance the tolerance against FOLFIRINOX-related adverse events. All patients in cohort were offered modified-FOLFIRINOX (2-weekly schedule) and evaluated every 4 cycles. Complete blood counts and other necessary blood tests were regularly performed every week. Biliary stenting and drainage procedures were performed in patients with jaundice. In our study, there were 13 patients underwent either chemotherapy or surgical resection before FOLFIRINOX. Six of them underwent tumor resection, four of them received chemotherapy, and the other three patients underwent both operation and chemotherapy. Once chemotherapy resistance or PD was observed, the modified-FOLFIRINOX was stopped. For those patients with SD or PR, the duration of FOLFIRINOX will be as long as 12 cycles and then take S1 orally. When S1 is not strong enough to control the disease, FOLFIRINOX is still the first choice for patients with good performance score.

Statistical analysis

All data were analyzed using SPSS software (version 22). Data were presented as median and range. PFS and OS analyses were performed using the Kaplan–Meier method and log-rank tests. A *P* value less than 0.05 was considered statistical significance.

Results

Patient characteristics

A total of 62 patients were finally included and received the modified-FOLFIRINOX treatment. The baseline characteristics are listed in Table 2. The range of age was 38–75, with a mean age of

Table 2
Patient characteristics at baseline.

Patients Characteristics	All Patients n = 62
Age-Mean (Range)	61.7 (38–75)
Gender-no.(%)	
Male	42 (67.7)
Female	26 (32.3)
Smoke-no.(%)	
No	36 (58.1)
Yes	26 (41.9)
Alcohol-no.(%)	
No	40 (64.5)
Yes	22 (35.5)
Presenting symptoms-no.(%)	
Jaundice	6 (9.7)
Pain	54 (87.1)
Weight loss	31 (50)
Co-morbidities-no.(%)	
Hypertension	17 (27.4)
Diabetes mellitus	12 (19.4)
Coronary heart disease	0
Chronic obstructive pulmonary disease	0
Other malignancy	0
ECOG performance score-no.(%)	
0	38 (61.3)
1	24 (38.7)
2	0
Pancreatic tumor location-no.(%)	
Proximal	22 (35.5)
Distal	40 (64.5)
Metastatic sites-no.(%)	
Liver	49 (79)
Lung	1 (1.6)
Peritoneal	7 (11.3)
Lymph node ^a	10 (16.7)
Others	5 (8.1)
Previous therapy	
Chemotherapy	7 (11.3)
Radiation	0
Curative intent procedures	9 (14.5)
Open-close surgery	1 (1.6)
Biliary stent	6 (9.7)
Lab tests ^b -Mean (Range)	
CA19-9 (U/mL)	5724.7 (2–12000)
Carcino-Embryonic Antigen (U/mL)	72.1 (1–1044)
Alpha-FetoProtein (ng/mL)	33.9 (1–1898)
Albumin (g/L)	39.4 (30–50)
Serum Creatinine (umol/L)	58.8 (30–104)
Total Bilirubin (umol/L)	21.4 (5–138)
Blood Platelet (10 ⁹ /L)	193.6 (40–361)
White Blood Cell (10 ⁹ /L)	6.9 (2.0–14.0)

^a Lymph node located in peri-aortic, caval, SMA and CA.^b The initial lab test results after admission.

61.7 years old. The majority of the patients (n = 38, 61.3%) demonstrated an ECOG score of 0. Fifty-four (87.1%) patients presented with abdominal pain when diagnosed, and six patients (9.7%) placed biliary stent or catheter before chemotherapy because of jaundice. The liver was the commonest organ with metastases found (n = 49, 79%). The baseline laboratory testing results, including CA19-9, CEA, AFP, albumin, serum creatinine, total bilirubin, blood platelet and white blood cell, after admission are also listed in Table 2. Fifty-four patients (87.1%) were found with elevated CA19-9 levels before chemotherapy.

Response

Forty patients (64.5%) were restaged after modified-FOLFIRINOX treatment. The response of these patients was evaluated and is shown in Table 3. Though no CR was observed, 13 (32.5%) patients showed PR. Unfortunately, 16 out of 40 (40%) had PD. We were able to evaluate CA19-9 response in 32 out of 54 patients with elevated

Table 3
Response to modified-FOLFIRINOX.

Variable	All patients n = 62
Could not be evaluated	22 (35.5)
Response-no.(%)	n = 40
Complete Response (CR)	0
Partial Response (PR)	13 (32.5)
Stable Disease (SD)	11 (27.5)
Progressive Disease (PD)	16 (40)
Rate of Objective Response (OR)-no.(%)	13 (32.5)
Rate of Disease Control (DC)-no.(%)	24 (60)

The Objective Response rate was defined as the percentage of patients with CR or PR.

The Rate of Disease Control was defined as the percentage of patients with CR, PR or SD.

pre-treatment CA19-9 results. A decrease in CA19-9 was observed in 25 patients (25/32, 78.1%) after four cycles of FOLFIRINOX. The median OS of patients with decreased CA19-9 levels was 14.0 months, while that of the others was only 7.0 months ($P < 0.01$; Fig. 1a). A temporary increase in CA19-9 level (more than 1.5 times compared to baseline) was observed in 11 patients from the decreased group. In addition, we found that the pre-treatment level of CA19-9 did not affect OS in patients with MPC (median OS of 10.5 and 10.3 months in CA19-9 normal and elevated groups respectively, $P = 0.78$; Fig. 1b).

Adverse events

In general, the incidence of adverse events was 80.6% (n = 50), and neutropenia was the most frequent one, with an incidence of 64.5%. For severe adverse events, we observed 27 patients (43.5%) with grade 3/4 toxicities, among which 29% (n = 18) was neutropenia, 4.8% (n = 3) was thrombocytopenia, 8.1% (n = 5) was anemia, 4.8% (n = 3) was infection, and 14.5% (n = 9) was elevated level of alanine aminotransferase (ALT; Table 4). Grade 3/4 vomiting was not observed in the present study, probably due to the combination therapy of ondansetron, azasetron and metoclopramide during the chemotherapy and removal of fluorouracil intravenous bolus from the regimen. No patients suffered febrile neutropenia, sensory neuropathy or thromboembolism. Totally, 43 patients (69.4%) received granulocyte-colony stimulating factor treatment before or after chemotherapy. Moreover, five patients (8.1%) required interleukin 11 therapy, and two patients (3.2%) were treated with thrombopoietin.

Survival

All 62 patients were included for survival analysis. The median number of treatment cycles was 5, ranging from 1 to 15. The median duration of follow-up was 7 (range 1–22) months. The median OS was 10.3 months, and a total of 32 (53.2%) patients died at the last follow-up. The median PFS of was 7.0 months (Fig. 2).

Discussion

MPC patients have extremely short survival, and few treatment modalities have been established in such clinical scenario. FOLFIRINOX chemotherapy can produce remarkable efficacy in MPC patients with significantly increased survival, compared to gemcitabine monotherapy [10], and is a promising strategy for these unfortunates. However, the application of FOLFIRINOX is largely limited by its considerable toxicity. As a consequent, clinicians in China hesitate to prescribe FOLFIRINOX for MPC patients, although it may have better efficacy to combat tumor. Very limited MPC

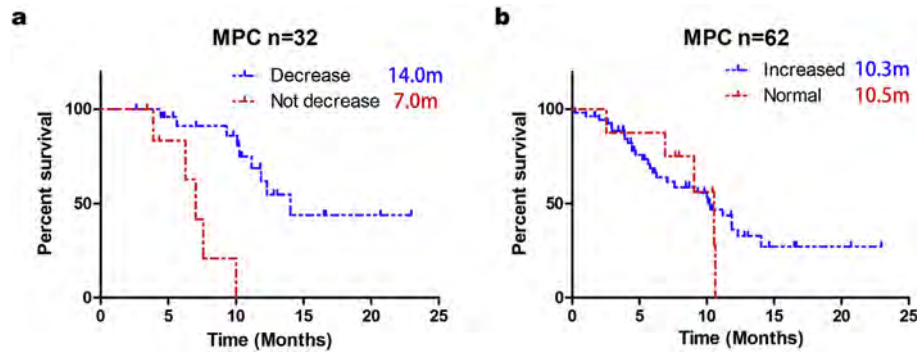


Fig. 1. The association between median OS and CA19-9 levels in MPC patients. a. Response was evaluated in 32 patients with elevated CA19-9 levels detected before chemotherapy. After four cycles of treatment, patients were divided into two groups according to the change of CA19-9 levels following chemotherapy. The median survival time of the decreased group ($n = 25$) was 14.0 months, and that of the others ($n = 7$) was 7.0 months ($P < 0.01$). b. The median OS of all patients was analyzed, according to the pre-chemotherapy CA19-9 level. No significant difference was observed between the normal ($n = 8$, 10.5 months) and elevated groups ($n = 54$, 10.3 months; $P = 0.78$).

Table 4
Adverse events.

Events	MPC	
	$n = 62$	
	Total	Grade 3/4
Hematologic-no.(%)		
Neutropenia	40 (64.5)	18 (29)
Febrile neutropenia	0	0
Thrombocytopenia	26 (41.9)	3 (4.8)
Anemia	35 (56.5)	5 (8.1)
Non-hematologic-no.(%)		
Infection	4 (6.5)	3 (4.8)
Fatigue	4 (6.5)	0
Vomiting	14 (22.6)	0
Diarrhea	2 (3.2)	0
Sensory neuropathy	0	0
Elevated level of ALT	28 (45.2)	9 (14.5)
Thromboembolism	0	0
Hematopoietin		
G-CSF	43 (69.4)	
IL-11	5 (8.1)	
TPO	2 (3.2)	
EPO	0	

Abbreviations: G-CSF, granulocyte-colony stimulating factor; IL-11, interleukin 11; TPO, thrombopoietin; EPO, erythropoietin.

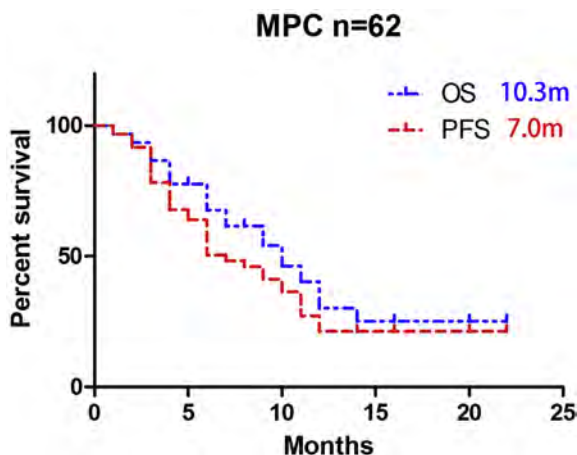


Fig. 2. Kaplan–Meier survival estimates of survival. A total of 62 patients were treated using modified-FOLFIRINOX. The median overall survival of all patients was 10.3 months, and the median progression-free survival was 7.0 months.

patients have tried FOLFIRINOX regimen in some Chinese institutions, and these studies were halted because of the poor tolerance.

To make FOLFIRINOX more practicable, many investigators have made their efforts to enhance patients' tolerance to this chemotherapy through various ways [13]. Mahaseth et al. significantly reduced the incidence of grade 3/4 neutropenia and diarrhea without compromising the efficiency of FOLFIRINOX simply by removing fluorouracil bolus and using hematopoietic growth factors at the same time [14]. Stein et al. reduced the doses of both irinotecan and fluorouracil bolus by 25%, and found that the incidences of neutropenia, vomiting and fatigue were significantly decreased [15]. Other modification strategy for advanced pancreatic cancer includes avoiding use of irinotecan [18] and it may be referential in MPC patients. However, all these attempts were made out of China. Due to the racial differences between Chinese and Western patients, the experience acquired from Western people may be not suitable for Chinese patients. Thus, appropriate modification of FOLFIRINOX is urgently needed in China. In the present study, we modified FOLFIRINOX by reducing oxaliplatin and irinotecan to 85% and 75% of the full dose, respectively, and abandoning fluorouracil intravenous bolus for the purpose of improving tolerability. Meanwhile, our modification maintained considerable efficacy of FOLFIRINOX, with an ORR of 32.5% and prolonged survival with acceptable toxicity.

Several studies have proven that modification of FOLFIRINOX did not compromise its efficacy. An American study recruiting 36 MPC patients treated with modified-FOLFIRINOX showed that median OS and PFS were 9.0 and 8.5 months, respectively [14]. Longer OS (median, 12.9 months) and PFS (median, 8.7 months) after modified-FOLFIRINOX treatment were also reported by another study with 66 MPC patients included [19]. In the current study, we enrolled 62 MPC patients and provided a novel modification strategy for FOLFIRINOX according to our experience. In our cohort, the median OS and PFS were 10.3 and 7.0 months, respectively, comparable to the previous studies. Furthermore, we found that the median OS of the patients with decreased CA19-9 levels was two-fold of that of the other patients after chemotherapy. Therefore, CA19-9 level after chemotherapy may be a prognostic indicator in MPC patients receiving modified-FOLFIRINOX. Since the pre-chemotherapy CA19-9 level did not influence OS in our study, the change of CA19-9 level more likely reflected tumor response to the treatment. Noticeably, a temporary increase of CA19-9 level was observed in some cases but it decreased after the following two cycles of treatment. Therefore, the elevation of CA19-9 level in the first two cycles may not suggest drug resistance.

Modified-FOLFIRINOX is also supposed to reduce adverse events. Conroy et al. reported that grade 3/4 adverse events with FOLFIRINOX treatment are neutropenia (45.7%), fatigue (17.8%), vomiting (14.5%), and diarrhea (12.7%) [9]. We showed that only 29% of patients receiving modified-FOLFIRINOX suffered grade 3/4 neutropenia, and no grade 3/4 fatigue, vomiting or diarrhea was observed at all. We believe that the removal of fluorouracil bolus from FOLFIRINOX and the use of hematopoietic growth factors contributed to the reduction of grade 3/4 neutropenia and diarrhea. The relatively low risk of hematological adverse events (thrombocytopenia and anemia) and none chemotherapy-related treatment cessation or death suggested a good tolerability of our modified-FOLFIRINOX regimen.

In summary, we showed that our modified-FOLFIRINOX was well tolerated in MPC patients, with an ORR of 32.5%, median OS of 10.3 month, and PFS of 7.0 months. Reduction of serum CA19-9 levels post-chemotherapy was associated with better prognosis. The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire may be needed to obtain better evaluation of quality of life of patients receiving modified-FOLFIRINOX treatment. To our knowledge, this is the first prospective study aiming to evaluate the efficacy of FOLFIRINOX in Chinese MPC patients, and they did benefit from dose reduction with improved safety and similar tumor response. More studies in Chinese population are required to validate these results and provide better modification of FOLFIRINOX regimen.

Acknowledgments

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Conflict of interest

The authors declare no potential conflict of interest.

References

- [1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2015, *CA Cancer J. Clin.* 65 (2015) 5–29.

- [2] H. Haeno, M. Gonen, M.B. Davis, J.M. Herman, C.A. Iacobuzio-Donahue, F. Michor, Computational modeling of pancreatic cancer reveals kinetics of metastasis suggesting optimum treatment strategies, *Cell* 148 (2012) 362–375.
- [3] D.P. Sohal, R.M. Walsh, R.K. Ramanathan, A.A. Khorana, Pancreatic adenocarcinoma: treating a systemic disease with systemic therapy, *J. Natl. Cancer Inst.* 106 (2014) dju011.
- [4] W. Chen, R. Zheng, P.D. Baade, S. Zhang, H. Zeng, F. Bray, et al., Cancer statistics in China, 2015, *CA Cancer J. Clin.* 66 (2016) 115–132.
- [5] J. Luo, L. Xiao, C. Wu, Y. Zheng, N. Zhao, The incidence and survival rate of population-based pancreatic cancer patients: Shanghai Cancer Registry 2004–2009, *PLoS One* 8 (2013), e76052.
- [6] M. Bockhorn, F.G. Uzunoglu, M. Adham, C. Imrie, M. Milicevic, A.A. Sandberg, et al., Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS), *Surgery* 155 (2014) 977–988.
- [7] H.A. Burris, M.J. Moore, J. Andersen, M.R. Green, M.L. Rothenberg, M.R. Modiano, et al., Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial, *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* 15 (1997) 2403–2413.
- [8] M. Di Marco, R. Di Cicilia, M. Macchini, E. Nobili, S. Vecchiarelli, G. Brandi, et al., Metastatic pancreatic cancer: is gemcitabine still the best standard treatment? (Review), *Oncol. Rep.* 23 (2010) 1183–1192.
- [9] M. Suker, B.R. Beumer, E. Sadot, L. Marthey, J.E. Faris, E.A. Mellon, et al., FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis, *Lancet Oncol.* 17 (2016) 801–810.
- [10] T. Conroy, F. Desseigne, M. Ychou, O. Bouché, R. Guimbaud, Y. Bécouarn, et al., FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer, *N. Engl. J. Med.* 364 (2011) 1817–1825.
- [11] G.F. Liu, G.J. Li, H. Zhao, Efficacy and toxicity of different chemotherapy regimens in the treatment of advanced or metastatic pancreatic cancer: a network meta-analysis, *J. Cell Biochem.* (2017 Jun 13), <http://dx.doi.org/10.1002/jcb.26210> (Epub ahead of print).
- [12] T. Conroy, C. Gavaille, E. Samalin, M. Ychou, M. Ducreux, The role of the FOLFIRINOX regimen for advanced pancreatic cancer, *Curr. Oncol. Rep.* 15 (2013) 182–189.
- [13] K.S. Gunturu, X. Yao, X. Cong, J.R. Thumar, H.S. Hochster, S.M. Stein, et al., FOLFIRINOX for locally advanced and metastatic pancreatic cancer: single institution retrospective review of efficacy and toxicity, *Med. Oncol.* 30 (2013) 361.
- [14] H. Mahaseth, E. Brucher, J. Kauh, N. Hawk, S. Kim, Z. Chen, et al., Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma, *Pancreas* 42 (2013) 1311–1315.
- [15] S.M. Stein, E.S. James, Y. Deng, X. Cong, J.S. Kortmansky, J. Li, et al., Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer, *Br. J. Cancer* 114 (2016) 737–743.
- [16] S.J. Rombouts, T.H. Mungroop, M.N. Heilmann, H.W. van Laarhoven, O.R. Busch, I.Q. Molenaar, et al., FOLFIRINOX in locally advanced and metastatic pancreatic cancer: a single centre cohort study, *J. Cancer* 7 (2016) 1861–1866.
- [17] E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), *Eur. J. Cancer* 45 (2009) 228–247.
- [18] H.A. El-Hadaad, H.A. Wahba, Oxaliplatin plus 5-fluorouracil and folinic acid (OFF) in gemcitabine-pretreated advanced pancreatic cancer: a phase II study, *J. Gastrointest. Cancer* 44 (2013) 313–317.
- [19] M.K. Chhanna, N. Cook, N.C. Dhani, K. Giby, A. Dodd, L. Wang, et al., FOLFIRINOX for advanced pancreatic cancer: the Princess Margaret Cancer Centre experience, *Br. J. Cancer* 115 (2016) 649–654.

Appendix LOWERY01

Meeting Abstract: 2012 ASCO Annual Meeting I

FREE ACCESS Gastrointestinal (Noncolorectal) Cancer May 20, 2012

Activity of front-line FOLFIRINOX (FFX) in stage III/IV pancreatic adenocarcinoma (PC) at Memorial Sloan-Kettering Cancer Center (MSKCC).

Authors: [Maeve A Lowery](#), [Kenneth H. Yu](#), [Nelly G. Adel](#), [Arlyn J. Apollo](#), [Michelle S. Boyar](#), [Philip Caron](#), [David Ilson](#), [Neil Howard Segal](#), [Yelena Yuriy Janjigian](#), [Diane Lauren Reidy](#), [Ghassan K. Abou-Alfa](#), and [Eileen Mary O'Reilly](#) | [AUTHORS INFO & AFFILIATIONS](#)

Publication: Journal of Clinical Oncology Volume 30, Number 15 suppl https://doi-org.myaccess.library.utoronto.ca/10.1200/jco.2012.30.15_suppl.4057

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Abstract

4057

Background: The PRODIGE/ACCORD trial recently established FFX as a treatment option for good performance status (PS) pts with stage IV PC (Conroy et al, NEJM 2011). We evaluated the activity and toxicity associated with FFX therapy in pts with advanced PC treated at MSKCC outside of a clinical trial. **Methods:** 80patients (pts) treated withFFX as 1st-line therapyat MSKCC between 07/1/10 and 12/30/11, were identified from an institutional database (prior IRB approval). Records were reviewed for demographic, treatment, toxicity, and response data. **Results:** 61 and 19 pts received FFX for stage IV and III PAC respectively. Demographics and outcomes are summarized in the table. Median starting dose of FFX was 80% of that used in the PRODIGE/ACCORD trial. Median overall survival (OS) was 12.5 months (mo) (95% CI 9.5–15.5) in pts treated with 1st line FFX for stage IV PAC and 13.7 mo (95% CI 11.3–15.8) in pts with stage III PAC. 68% of pts with stage IV PAC who discontinued FFX for disease progression (PD) or toxicity received 2nd-line gemcitabine-based therapy. **Conclusions:** We observed activity and acceptable toxicity in carefully selected patients treated with FFX at 80% dose intensity and routine use of growth factor support. Treatment with FFX resulted in median OS of > 1 year in pts with stage IV PAC and is an active front-line regimen.

	1st line: Stage IV N=61	1st line: Stage III N=19
Age (yrs)	64 (range 46-80)	58 (range 37-69)
Sex	-	-
Male	33(54%)	11(58%)
Female	28(46%)	8(42%)

	1st line: Stage IV N=61	1st line: Stage III N= 19
Primary tumor	-	-
Head	23(38%)	14(74%)
Body	21(34%)	2(10%)
Tail	17(28%)	3(16%)
Prophylactic growth factor	51(84%)	15(79%)
Median number of cycles	7	6
Dose reduction/discontinuation for toxicity	32(52%)	9(47%)
GI	11(18%)	4(21%)
Myelosupression	4(7%)	1(5%)
Neuropathy	9(15%)	1(5%)
Drug reaction	4(7%)	1(5%)
Other	4(7%)	2(10%)
Subsequent surgery/RT	N/A	1(5%)/10(53%)
Best response*	-	-
PR	21(40%)	4(21%)
SD	23(45%)	13(68%)
PD	8(15%)	2(11%)

COLLAPSE

* Evaluable pts N=52 (1 pt not yet staged, 3 pts< 2 cycles FFX due to toxicity/5 pts due to non-treatment-related death).

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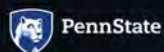
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Appendix MARSH02

REVIEW

Pancreatic cancer and FOLFIRINOX: a new era and new questions

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Keywords

Chemotherapy, FOLFIRINOX, genomics, modifications, pancreatic cancer, toxicity

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Abstract

FOLFIRINOX (FFX) was introduced to clinical practice in 2010 following publication of the PRODIGE 4/ACCORD 11 study, which compared this novel regimen to gemcitabine in metastatic pancreatic cancer. Median overall survival, progression-free survival, and objective responses were all superior with FFX and there was improved time to definitive deterioration in quality of life. Despite initial concerns over toxicity, there has been rapid uptake of this regimen, both revolutionizing management and opening the door to innovative research. As experience with FFX has accrued, many questions have arisen including the management of toxicities, the impact of frequent modifications, the optimal number of cycles, integration with other regimens and modalities, interpretation of radiologic and serologic response, utility of molecular signatures, and potential benefit in unique clinical settings such as pre- and postsurgery. This review will closely examine these issues, not only to summarize current knowledge but also to fuel scientific debate.

Introduction

Historical context

Previously published studies have suggested that combination therapy could be an improvement on gemcitabine alone. These include the phase III study of gemcitabine versus gemcitabine plus erlotinib [1], the phase III study of gemcitabine versus gemcitabine plus capecitabine [2], and the phase II study of GTX (gemcitabine, taxotere, and capecitabine) [3, 4]. In the first study, overall survival (OS) (median 6.24 vs. 5.91 months, HR = 0.82, 95% CI = 0.69–0.99; $P = 0.038$), 1-year survival (23% vs. 17%; $P = 0.023$), and progression-free survival (HR = 0.77, 95% CI = 0.64–0.92; $P = 0.004$) were better with gemcitabine plus erlotinib. In the second study, objective response rate (19.1% vs. 12.4%; $P = 0.034$) and progres-

sion-free survival (HR = 0.78; 95% CI = 0.66–0.93; $P = 0.004$) favored the combination and there was a trend toward improved OS (7.1 vs. 6.2 months, HR = 0.86, 95% CI = 0.72–1.02; $P = 0.08$). In the GTX study, median progression-free survival of responders was 6.3 months (95% CI = 4.4–10.4 months) and median survival was 11.2 months (95% CI = 8.1–15.1 months). While certainly of interest, the clinical benefit of these regimens was either marginal, of uncertain impact on quality of life, or achieved in very small numbers, resulting in sporadic and unenthusiastic uptake.

FOLFIRINOX

Promising phase II results with FOLFIRINOX (FFX) [5] (oxaliplatin 85 mg/m², leucovorin 400 mg/m², irinotecan 180 mg/m², bolus 5-fluorouracil 5FU) (400 mg/m², infu-

sional 5FU 2400 mg/m² over 46 h, every 14 days) were confirmed in a sentinel phase III study (PRODIGE 4/ACCORD 11) [6], which randomized patients ≤75 years of age with metastatic pancreatic cancer and an ECOG PS of 0 or 1, to receive either gemcitabine or FFX. With a median follow-up of 26.6 months and with 171 patients in each arm (38% of patients had lesions in the head of the pancreas with 14.3% requiring biliary stents), the median survival with FFX was 11.1 months versus 6.8 months for gemcitabine ($P < 0.001$, HR = 0.57, 95% CI = 0.45–0.73). More impressively, 1-year survival was 48.4% versus 20.6%, respectively, and this difference was sustained at 18 months, 18.6% versus 6%. Quality of life measures, equally, strongly favored the FFX group [7].

While toxicity was not inconsequential (45.7% grade 3 or 4 neutropenia, 5.4% febrile neutropenia, 12.7% diarrhea, 9.1% thrombocytopenia, 9.0% sensory neuropathy), oncologists rapidly adopted the FFX regimen following the 2010 ASCO meeting [8]. Many questions have now arisen such as: best management of common and uncommon toxicities; potential impact of adjustments to the original regimen; number of cycles administered for optimal results; innovative strategies in early disease; radiologic and serologic assessment of response; evolving data on integration into overall treatment planning; and utility of molecular profiling.

In order to derive the data used in this review, all relevant papers in Medline, CANCERLIT, and Index Medicus together with meeting abstracts from ASCO, ASTRO, and AACR since 1990, were examined. No ethnic or racial group or gender was excluded. Approximately 65% of discovered references have been included based on relevance, timeliness, and quality of data.

How is Toxicity of FFX Best Managed?

As with usual practice, reduction in individual drug dosing is a standard approach for many of the common

complications such as low blood counts, fever, infection, diarrhea, weight loss, and fatigue. However, some problems engendered by FFX are either idiosyncratic, not dose related, or not manageable with simple dose reduction and may require more innovative strategies (Table 1).

If platelet counts are problematic despite dose modifications, then splenectomy, either surgical [9] or by endovascular means using an embolic approach [10], can help in selected patients. The typical phenotype would be someone who is responding to chemotherapy, with a good functional status, but who has isolated thrombocytopenia ($<90 \times 10^3/\mu\text{L}$). In the surgical series, counts increased significantly ($P < 0.01$) with a mean value of $87 \times 10^3/\mu\text{L}$ prior to treatment and $425 \times 10^3/\mu\text{L}$ on discharge (average 3 days later). All patients were able to resume chemotherapy within a median of 11.5 days (range 6–27). The IR procedure could be particularly useful in those either too frail for surgery or for whom surgery is relatively contraindicated (e.g., disease in the splenic hilum or carcinomatosis). Complications of post-operative pain and splenic abscess are limiting factors [11] and relative efficacy is unknown.

Infusion reactions are common and desensitizing protocols may be needed [12]. A significant hypercholinergic response with excess salivation, cramping, and sweating, related to the piperidine structure of irinotecan, which mimics a cholinergic drug when metabolized by esterases to form SN-38, is not unusual [13]. The potentiating role of oxaliplatin is real but not well understood [14]. Slowing of the infusion, aggressive medication with atropine, and a proton pump inhibitor may be required.

The common problems of oral dysesthesia and thick tongue, and the rare complication of total body weakness, near paralysis and even coma from oxaliplatin may be difficult to manage. Slowing the infusion and a warm drink works best for the former, while aggressive correction of serum potassium and calcium prior to, and following, the infusion may resolve the latter [15, 16].

Table 1. Management of FOLFIRINOX toxicity.

Toxicity	Strategy	Concern
Low blood counts, fatigue, diarrhea, mucositis	Decrease doses of one or more of the drugs; lomotil/pegfilgrastim	Decreased efficacy of therapy; bone pain
Low platelet counts despite appropriate dose reduction	Splenectomy—surgical or via interventional radiology	Pain; abscess formation; treatment delay
Acute allergic reaction to oxaliplatin infusion	Desensitization protocol and possible discontinuation	Ineffective to resolve problem; resources
Hypercholinergic reaction with cramping and sweating	Slow infusion rate and premedicate with atropine	Prolonged treatment time; resources
Oral dysesthesia with sense of swollen tongue	Slow infusion rate and warm drink	Prolonged treatment time; anxiety; resources
Weakness, paralysis, and even coma	Maintenance of normal potassium and calcium prior to and during infusion	Patient anxiety; staff anxiety; imperfect results

Do Modifications to the FFX Regimen Matter?

Oncologists in the United States and elsewhere were anxious to use FFX, but initially concerned about toxicity, particularly in patients with lesions in the head of the pancreas and with biliary stents. A Canadian report suggested that there could be considerable toxicity when the regimen is used outside of a clinical study and in community centers [17]. In their series of 46 patients, there were 3 (7%) treatment-related deaths, 54% of patients were hospitalized with sepsis, 33% had neutropenia grade ≥ 3 , 15% had diarrhea grade ≥ 3 , and 4 (9%) patients had febrile neutropenia.

With this scenario in mind, many modifications have been made (Table 2). Initially, physicians removed the bolus of 5FU, which is notably myelosuppressive, with some adding pegfilgrastim 6 mg on day 3 or 4. Commonly referred to as “mFOLFIRINOX,” this seems to be the way it is often used today [18]. Historically, a bolus of 5FU has been used in the majority of fluoropyrimidine regimens, together with a more prolonged infusion to maximize total exposure [19]. A Japanese study shows that the bolus contributes significantly to the overall exposure to 5FU via AUC [20]. In addition, 5FU functions differently depending on how it is administered [21] and thus, theoretically, the omission of the bolus could lead to loss of efficacy. Data reported at the 2014 GI ASCO meeting suggest, however, that this may not be

the case, and longer follow-up will be needed for clarification [22].

A further dilemma concerns the omission of leucovorin, should the bolus of 5FU be removed. Previous dose-finding studies of infusional 5FU with leucovorin clearly demonstrated that there is considerable synergy, and that omission of leucovorin results in less toxicity [23], suggesting that efficacy could equally be impacted. Absent real data, and given the low cost of leucovorin, it seems reasonable to leave it untouched.

Ohio State physicians reported their experience with limiting irinotecan to 165 mg/m² in addition to these changes, in either locally advanced or borderline resectable disease. They concluded that the modified regimen was effective and well tolerated with no episodes of grade 3 or 4 neutropenia/thrombocytopenia, but with 46% of patients requiring a dose reduction for other toxicities [24]. Similarly, physicians at Yale reported that in their hands dose reductions were common (relative dose intensities: oxaliplatin 88%, irinotecan 64%, bolus 5FU 57%, infusional 5FU 100%, compared to oxaliplatin 78%, irinotecan 81%, and 5FU 82%—PRODIGE 4/ACCORD 11) [25]. Despite these modifications, efficacy was comparable to that of the original regimen—response (CR + PR 33%—similar to historical data 31.6%; $P = 0.21$), and toxicity was notably less (grade 3 or 4 neutropenia 6.4%, $P < 0.0001$; fatigue 9.6%, $P < 0.02$).

For frail and elderly patients, additional adjustments have been made. In a series of 19 patients over age 65,

Table 2. FOLFIRINOX dose modifications and results.

Author	Modification	Results/comments
Mahaseh et al. [18]	Drop 5FU bolus Add pegfilgrastim 6 mg	Grade 4 neutropenia 3% Grade 3/4 diarrhea 13%, fatigue 13% OS 9.0 months, PFS 8.5 months
Blazer et al. [24]	Drop 5FU bolus Decrease irinotecan to 165 mg/m ² Add pegfilgrastim 6 mg	Grade 3/4 neutropenia or thrombocytopenia 0% 46% further dose reductions for other toxicities
Gunturu et al. [25]	Median dose intensity 5FU bolus 57% Median dose intensity oxaliplatin 88% Median dose intensity irinotecan 64%	Grade 3/4 neutropenia 6.4% Grade 3/4 fatigue 9.6% CR plus PR 31.6%
Metges et al. [27]	Median dose intensity 5FU bolus 82% Median dose intensity oxaliplatin 78% Median dose intensity irinotecan 81%	Grade 3/4 hematologic and neurotoxicity 32% Response rate 39% PFS 6.5 months OS 10.9 months
Alessandretti et al. [26]	Drop 5FU bolus Decrease 5FU infusion to 2000 mg/m ² Decrease oxaliplatin to 50 mg/m ² Decrease irinotecan to 135 mg/m ² Add pegfilgrastim 6 mg	Grade 3/4 neutropenia 21% or thrombocytopenia 5% Grade 3/4 fatigue 15.7% CR plus PR 31.7% OS and PFS not reached at 4 months
James et al. [22]	Decrease 5FU bolus 25% Decrease irinotecan 25% Add pegfilgrastim 6 mg	Grade 3/4 neutropenia 17% or thrombocytopenia 11.3% Grade 3/4 fatigue 11.3% CR plus PR 29%

the bolus of 5FU was dropped and doses of both oxaliplatin and irinotecan were lowered (5FU 2000 mg/m² over 46 h, oxaliplatin 50 mg/m², irinotecan 135 mg/m²) [26]. Grade 3/4 toxicities were reported in 10 patients: nausea/vomiting in one, diarrhea in one, fatigue in three, neutropenia in four, thrombocytopenia in one, and febrile neutropenia in three—all manageable. A follow-up study by the original investigators in the PRODIGE 4/ACCORD 11 study, based on their established criteria, showed that 81% of 242 patients required a dose reduction, but that this did not affect results (response rate 39% vs. 32%, PFS 6.5 vs. 6.4 months and OS 10.9 vs. 11.1 months) [27].

A biologically based refinement, using genotype-derived dosing of irinotecan via UGT1A1, the enzyme that inactivates SN-38 (the active metabolite of irinotecan) showed that those with a *28/*28 genotype are at highest risk of severe neutropenia, *1/*28 at intermediate risk, and *1/*1 at lowest risk [28]. Initial doses of irinotecan could be adjusted accordingly.

A close examination of clinicaltrials.gov confirms that the majority of regimens presently under investigation incorporate some modification of FFX.

How is the Number of Treatment Cycles with FFX Determined?

The optimal number of treatment cycles is not well understood, but the goal of therapy (i.e., curative vs. palliative) is critical in this regard. The disease should be unambiguously defined as either resectable, borderline resectable, locally advanced unresectable, or metastatic. This has implications for ensuring that treatment is not unnecessarily modified, or conversely, that excessive treatment (and toxicity) is not given. This is simplest in a palliative setting, where duration and intensity of treatment is determined by response and quality of life. The median number of cycles in the original PRODIGE 4/ACCORD 11 study was 10, with a range of 1–47 [6]. In locally advanced and borderline resectable disease, it is common to use four cycles of FFX ($\pm$ chemo/RT) in a neoadjuvant strategy (e.g., ALLIANCE/Intergroup study A021101). This is based on very limited data, and an alternative approach might be to treat to maximal response and/or maximum-tolerated dose. A retrospective study of this strategy in borderline (60%) and locally advanced, unresectable (40%) disease examined outcomes in 18 patients [29]. An R0 resection was ultimately possible in 44% of patients, with a median number of six cycles (range 5–17) prior to surgery. A report on FFX plus chemo/RT in 22 patients with locally advanced, unresectable disease, examined use of an initial four cycles with an additional four cycles prior to chemo/RT, if disease was either stable or

improved [30]. A median of eight cycles was administered, with 12 patients taken to the OR and 5 (42%) were able to have an R0 resection. However, three patients developed distant recurrence within 81 days, confirming their dismal prognosis.

Steatohepatitis (irinotecan) and sinusoidal obstructive syndrome (oxaliplatin) are dose-related complications which effect outcome in liver resection for colorectal cancer [31]. A Whipple operation, in and of itself, leads to an increase in hepatic steatosis [32]. Further, a BMI exceeding 25 kg/m², diabetes mellitus, and preexisting steatosis all significantly increase the risk of steatohepatitis and postoperative morbidity [33]. These data suggest that the number of cycles be limited to the minimum necessary, as the effects on patients undergoing a Whipple operation are as yet unknown.

Complicating matters further, pancreatic cancer is clearly a heterogeneous disease [34]. Aggressive subsets (if they do respond) may require three or four cycles of therapy before showing a decline in CA 19-9, implying response, and may conceivably require further cycles of chemotherapy prior to surgery.

In locally advanced (arterial encasement) or metastatic disease, initial intensive therapy could be followed by omission of either oxaliplatin or irinotecan (depending on which is more problematic) for continuation of a “maintenance program,” as this is strictly palliative therapy. While there are few publications on the efficacy of FOLFOX or FOLFIRI, those that do exist are positive [35–37].

Is Preoperative or Postoperative FFX the Optimal Strategy for Potentially Resectable Disease?

One of the most intriguing questions currently under study is whether FFX will improve on results in the adjuvant therapy of resectable pancreatic cancer. A recent update of the CONKO-001 study shows that median OS is 22.8 months in the gemcitabine group versus 20.2 months in the observation group (HR = 0.76, P = 0.01) [38]. OS at 5 and 10 years is 20.7% versus 12.2% and 10.4% versus 7.7%, respectively—all dismal numbers.

Studies comparing gemcitabine with combination therapy, and even vaccine therapy, have failed to improve on these results [39–41]. There are no data as yet on FFX in the adjuvant setting (PRODIGE 24/ACCORD 24—gemcitabine vs. mFFX; and Marsh et al.—four cycles of mFFX pre- and postsurgery, are in progress) (clinicaltrials.gov). The latter approach is intriguing as early systemic treatment, prior to surgical intervention, is attractive for many reasons: better selection of patients for surgery based on the exclusion of those with rapidly progressive disease; better tumor exposure to chemotherapy prior to disrup-

tion of the vasculature; ability to gauge response; better tolerance of chemotherapy prior to debilitating surgery; and increased R0 resections. Furthermore, pancreatic cancer has been shown to be systemic from the earliest stages [42–44] and thus an early systemic approach is not only logical but may also be essential.

Previous studies of neoadjuvant therapy in resectable patients include gemcitabine plus radiation (73/86 were taken to surgery, with 64/86 undergoing successful surgery) [45]; and gemcitabine plus nab-paclitaxel (14/25 completing the planned three cycles, with surgery in 20/25, 19/20 R0) [46]; (9/16 undergoing surgery at the time of reporting, with 8/9 R0 resections) [47].

The University of Michigan reported improved 1- and 3-year OS, lower margin and node positivity, and minimal additional perioperative toxicity in a retrospective review of various neoadjuvant regimens in borderline resectable disease [48]. University of Washington similarly reported almost doubling of OS in a small series of patients with both resectable and borderline resectable disease (neoadjuvant GTX vs. historical controls) [49], and Columbia was able to convert 57% of inoperable patients to operable with 49% R0 resections [50]. Finally, the Medical College of Wisconsin reported on mFFX followed by radiation therapy in borderline resectable disease and found this approach both safe and favorable compared to historical controls [51]. The ALLIANCE/Intergroup A021101 study is examining the feasibility of mFFX for four cycles followed by RT with oral capecitabine in a multi-institutional setting. Gemcitabine is given in the adjuvant space. The primary endpoint is 1-year OS and there are multiple levels of quality control to ensure validity (clinicaltrials.gov).

How Best Can Response to FFX Therapy be Assessed?

Both serologic and radiographic response to therapy has come under increasing scrutiny. CA 19-9 has been used for decades as a serum marker in pancreatic cancer in Lewis antigen-positive individuals [52, 53]. However, this is complicated by the fact that biliary obstruction, pancreatitis, intestinal inflammation, and even elevated blood glucose [54] all lead to an increase in CA 19-9. While there is evidence that there is a difference in outcome between no responders and stable or good responders [55, 56], there are opposing findings suggesting that there may be no correlation [57], and additional data are awaited.

Change in tumor dimensions, as assessed on CT scan and/or MRI, is both challenging to measure and often insignificant [58]. In a study of 129 patients with borderline resectable tumors, post therapy, presurgical imaging suggested that only 1% had been down staged, 78% had

no change, and 21% had progressive disease [59]. In fact, 66% were able to undergo resection with 95% R0 resections. Provided the patient has acceptable performance status and no evidence of metastatic disease, even where there is no obvious radiographic response, surgery should proceed as pathology may indicate clear-cut treatment effect [60]. Whether pathologic response has any meaning in the clinical context awaits further clarification, but initial reports suggest that more than 5% viable cells in the final specimen portends a bad outcome [61, 62].

While endoscopic ultrasound can be valuable [63], novel ways of imaging the tumor, such as perfusion imaging [64], dynamic PET scans [65] and routine CT scan derived mass transport parameters, are increasingly being incorporated into investigational algorithms [66].

How is FFX Optimally Combined with Radiation Therapy?

Many protocols in borderline and locally advanced, unresectable disease switch to radiation therapy following initial FFX [51]. However, the precise role of radiation in these settings is the subject of ongoing debate. The LAP 07 study found that in locally advanced disease, chemo/radiation had no effect on OS compared to continued chemotherapy alone (over 40% of patients developed metastatic disease prior to being randomized to radiation or not) in those patients stable after an initial phase of gemcitabine $\pm$ erlotinib [67]. Updated results in 2014 suggested less local recurrence in the CRT arm (34% vs. 65%, $P < 0.0001$). The true impact of radiation may not be fully evaluable until systemic disease control improves further. An upcoming study will re-explore this question: the three-arm randomized phase II RTOG 1201 study, which is evaluating systemic chemotherapy alone (gemcitabine plus nab-paclitaxel) versus capecitabine plus standard versus intensified local RT (50.4 Gy vs. 63 Gy) preceded and followed by systemic therapy. Given that FFX is notably more active than gemcitabine in metastatic disease [6], the combination of radiation with FFX deserves to be examined and novel approaches such as SBRT [68, 69], may make it possible to do so.

How Best to Combine FFX with Other Regimens?

Recently, the MPACT study reported on gemcitabine plus nab-paclitaxel (GN) versus gemcitabine in 861 patients with metastatic pancreatic cancer [56]. Median OS was 8.5 versus 6.7 months (HR for death, 0.72; 95% CI = 0.62–0.83; $P < 0.001$), and progression-free survival was 5.5 versus 3.7 months (HR = 0.69, 95% CI = 0.58–0.82; $P < 0.0001$). While less than that of FFX in the

Table 3. Selected current studies using FOLFIRINOX in all stages of pancreatic cancer.

Setting	Study	Regimen	Goal	Opened
Resectable neoadjuvant	NorthShore/University of Chicago Pilot study	mFFX—no 5FU bolus—four cycles pre- and postop	Assess safety and efficacy (R0, ORR, PFS, and OS)	August 2012
Resectable neoadjuvant	Indiana University Phase II study	Standard full dose FFX—four cycles preoperatively	Assess safety and efficacy (Path CR, DFS, OS, ORR)	June 2014
Resectable neoadjuvant	Yale/NCI Phase II study	mFFX—no 5FU bolus—six cycles pre and post op	Assess safety and efficacy (R0, path CR, PFS, and OS)	January 2014
Resectable adjuvant	PRODIGE 24/ACCORD 24 Phase III	mFFX—no 5FU bolus—versus gemcit, each for 24 weeks	DFS, OS, specific survival	February 2012
Resectable adjuvant	Krankenhaus Nordwest Phase I/II	Standard full dose FFX—six cycles pre and postop vs. gemcit postop	Assess safety and efficacy (OS, PFS, R0, path CR)	Opening pending
Resectable adjuvant	Sidney Kimmel Comprehensive Cancer Center	SBRT plus Vaccine (GVAX)/cyclophosphamide then standard full dose FFX—six cycles with GVAX	Toxicity, safety, OS, DFS, TTF	April 2012
Borderline resectable	Pilot Study ALLIANCE A021101	mFFX—no 5FU bolus—four cycles, then RT/capecit	Accrual rate, toxicity, CR/PR, completion of all therapy, R0/R1	March 2013
Borderline resectable	Pilot study Medical University of South Carolina	mFFX—no 5FU bolus—six cycles then RT/capecit	R0/R1 resection (OS, TTR, ORR, path CR) and safety	August 2012
Borderline resectable	University of Maryland Pilot Study	mFFX—no 5FU bolus—four cycles then SBRT	Resectability, DFS, OS, TTR, path CR and safety	September 2013
Locally advanced	UNC LINEBERGER Phase II	Standard full dose FFX	Assess safety and efficacy (OS, PFS, ORR)	September 2012
Locally advanced	Foundation for Liver Research/Erasmus Medical Center Phase II	Standard full dose FFX—four cycles then SBRT	OS, radiologic RR, Resection rate, PFS, Biologic predictive markers	July 2014
Locally advanced	Massachusetts General Hospital/NCI Phase II	Standard full dose FFX—eight cycles plus losartan then proton beam RT	Feasibility, PFS, OS, toxicity, downstaging, gene mutations	March 2013
Metastatic disease	University of Chicago Phase II	Modified FFX—irinotecan dose determined by UGT1A1 status; no 5FU bolus	DLT in course 1; RR, cumulative dose intensity of irinotecan	July 2012
Metastatic disease	Institut Cancerologie de l'Ouest Phase II	Modified FFX—irinotecan dose determined by UGT1A1 status; 5FU dose by DPD expression	Safety, toxicity and efficacy (OS, PFS)	May 2014
Metastatic disease	Centre Val d'Aurelle—Paul Lamarque Phase I–II	Standard Gemcitabine plus nab-paclitaxel followed by standard FFX	MTD; Phase II dosing; RR	August 2013

ORR, overall response rate; PFS, progression-free survival; OS, overall survival; CR, complete remission; gemcit, gemcitabine; SBRT, stereotactic body radiation therapy; TTF, time-to-treatment failure; capec, capecitabine; TTR, time to response; DLT, dose-limiting toxicity; DPD, dihydropyrimidine dehydrogenase; MTD, maximum-tolerated dose; FFX, FOLFIRINOX; postop, postoperative.

PRODIGE 4/ACCORD 11 study—11.1 months [6], median OS is significant enough to be of major interest, raising the issue of how best to integrate these two regimens in a comprehensive treatment plan. One of the more interesting questions is whether there is synergism, and whether pretreatment with GN would alter the cancer-associated stroma such that FFX would be more effective. A recent phase II study used up to six cycles of GN followed by consolidation with FFX for up to 12 cycles and was deemed feasible [70]. A case report from Germany, reported success with this approach in locally advanced disease [71].

The efficacy of GN following failure of FFX is unknown. In a retrospective study from Yale, 23 patients were so treated with an estimated time-to-treatment failure of 11 weeks, about half of that in first-line GN [72]. Interestingly, dose densities of only 56.9% and 63.5% for nab-paclitaxel and gemcitabine, respectively, were achieved which suggest that alternative dosing schedules should be examined.

Innovative approaches currently under investigation include addition of a Hedgehog inhibitor to FFX [73]; combination of FFX, SBRT, and GVAX as adjuvant therapy; and a combination of FFX and hyperacute vaccine in borderline and locally advanced disease. As we learn more, it is hoped that future study design will be based on biology and molecular profiling of tumors, rather than empiricism or intuition.

How Do We Use Molecular Signatures in Planning FFX Treatment?

There is an increasing interest in the molecular profiling of cancers. Certainly, patients testing positive for a BRCA 1 or BRCA 2 mutation might have increased sensitivity to a platin [74], but this has uncertain practical value. PARP inhibitors might be more effective [75]. From the Pancreatic Cancer Genome Project, we know that pancreatic cancers contain an average of 63 genetic alterations, the majority of which are point mutations [76]. A core set of 12 cellular signaling pathways and processes are defined by these alterations in 67–100% of tumors. KRAS, Hedgehog, Wnt/Notch, SMAD4, and TGF- β signaling pathways are key, with abnormalities of one or more of these pathways in 100% of cancers. The effects on therapy with FFX are as yet unknown.

Candidates for future study include predictors of drug metabolism and toxicity—ERCC1 expression (oxaliplatin) [77], UGT 1A1 genotype (irinotecan) [28], thymidylate synthase expression (5FU) [78], HENT-1 expression (gemcitabine—both positive and negative studies) [79, 80] and SPARC expression—both nab-paclitaxel [81] and gemcitabine [82].

What Important Clinical Studies are Currently Underway in Pancreatic Cancer Using FFX Alone or in Combination?

As a final note, it is relevant to include a table of selected current and ongoing studies using FFX in all stages of pancreatic cancer (Table 3). These studies have been selected from many for their potentially significant impact on the use of this regimen in the future. It may once again be noted that FFX is very frequently modified.

Summary

FFX has had a major impact on the treatment of pancreatic cancer. As experience with this regimen has accrued, and as we have learned how to manage the toxicities, we have been presented with a new set of questions: the effect of frequent modifications; optimal use in all stages of pancreatic cancer; integration with both established and emerging therapies; how to evaluate response; and the incorporation of evolving molecular data. Furthermore, while metastasectomy in pancreatic cancer has historically been fraught with futility and failure, the markedly improved activity of FFX [5, 6] could mean that the time to study surgery plus FFX (in highly selected patients) is near [83, 84]. The next few years should prove to be exciting for all working to improve the outlook for this challenging group of patients.

Conflict of Interest

None declared.

References

1. Moore, M. J., D. Goldstein, J. Hamm, A. Figer, J. R. Hecht, S. Gallinger, et al. 2007. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J. Clin. Oncol.* 25:1960–1966.
2. Cunningham, D., I. Chau, D. D. Stocken, J. W. Valle, D. Smith, W. Steward, et al. 2009. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J. Clin. Oncol.* 27:5513–5518.
3. Fine, R. L., D. R. Fogelman, S. M. Schreiber, M. Desai, W. Sherman, J. Strauss, et al. 2008. The gemcitabine, docetaxel, and capecitabine (GTX) regimen for metastatic pancreatic cancer: a retrospective analysis. *Cancer Chemother. Pharmacol.* 61:167–175.
4. Dakik, H. K., D. J. Moskovic, P. J. Carlson, E. P. Tamm, W. Qiao, R. A. Wolff, et al. 2012. The use of GTX as

- second-line and later chemotherapy for metastatic pancreatic cancer: a retrospective analysis. *Cancer Chemother. Pharmacol.* 69:425–430.
5. Ychou, M., F. Desseigne, R. Guimbaud, M. Ducreux, O. Bouche, Y. Becouarn, et al. 2007. Randomized phase II trial comparing FOLFIRINOX (5FU/leucovorin [LV], irinotecan [I] and oxaliplatin [O]) vs gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma (MPA). First results of the ACCORD 11 trial. *ASCO Meeting Abstr.* 25(Suppl. 18): 4516.
 6. Conroy, T., F. Desseigne, M. Ychou, O. Bouche, R. Guimbaud, Y. Becouarn, et al. 2011. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N. Engl. J. Med.* 364:1817–1825.
 7. Gourgou-Bourgade, S., C. Bascoul-Molle, F. Desseigne, M. Ychou, O. Bouche, R. Guimbaud, et al. 2013. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. *J. Clin. Oncol.* 31:23–29.
 8. Bendell, J., S. Britton, M. Green, J. Willey, K. Lemke, J. Marshall. 2011. Immediate impact of the FOLFIRINOX phase III data reported at the 2010 ASCO Annual Meeting on prescribing plans of American oncology physicians for patients with metastatic pancreas cancer. *J. Clin. Oncol.* 29:2011 (suppl 4; abstr 286).
 9. Donahue, T. R., K. K. Kazanjian, W. H. Isacoff, H. A. Reber, and O. J. Hines. 2010. Impact of splenectomy on thrombocytopenia, chemotherapy, and survival in patients with unresectable pancreatic cancer. *J. Gastrointest. Surg.* 14:1012–1018.
 10. Kauffman, C. R., A. Mahvash, S. Kopetz, R. A. Wolff, J. Ensor, and M. J. Wallace. 2008. Partial splenic embolization for cancer patients with thrombocytopenia requiring systemic chemotherapy. *Cancer* 112:2283–2288.
 11. Wang, H. Y., S. C. Shih, S. C. Lin, W. S. Chang, T. E. Wang, F. J. Lin, et al. 2008. Partial splenic embolization: 12-month hematological effects and complications. *Hepatogastroenterology* 55:1838–1842.
 12. Gammon, D., P. Bhargava, and M. J. McCormick. 2004. Hypersensitivity reactions to oxaliplatin and the application of a desensitization protocol. *Oncologist* 9:546–549.
 13. Dodds, H. M., J. F. Bishop, and L. P. Rivory. 1999. More about: irinotecan-related cholinergic syndrome induced by coadministration of oxaliplatin. *J. Natl. Cancer Inst.* 91:91–92.
 14. Krexner, E., A. Stickler, C. Prainer, and J. Finsterer. 2012. Acute, generalised but transient muscle cramping and weakness shortly after first oxaliplatin infusion. *Med. Oncol.* 29:3592–3593.
 15. De Marco, S., E. Squilloni, L. Vigna, M. F. Bertagnolio, and C. N. Sternberg. 2004. Irinotecan chemotherapy associated with transient dysarthria and aphasia. *Ann. Oncol.* 15:1147–1148.
 16. Basso, M., A. Cassano, A. Modoni, D. Spada, N. Trigila, M. Quirino, et al. 2008. A reversible coma after oxaliplatin administration suggests a pathogenetic role of electrolyte imbalance. *Eur. J. Clin. Pharmacol.* 64:739–741.
 17. Amireault, C., J. Beaudet, G. Gaudet, N. Raymond, J.-P. Ayoub, R. Letourneau, et al. 2014. FOLFIRINOX in the real-world setting: the multicentric experience of six Canadian institutions. *ASCO Meeting Abstr.* 32(Suppl. 3): 367.
 18. Mahaseth, H., E. Brucher, J. Kauh, N. Hawk, S. Kim, Z. Chen, et al. 2013. Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. *Pancreas* 42:1311–1315.
 19. De Gramont, A., M. Krulik, J. Cady, B. Lagadec, J. E. Maisani, J. P. Loiseau, et al. 1988. High-dose folinic acid and 5-fluorouracil bolus and continuous infusion in advanced colorectal cancer. *Eur. J. Cancer Clin. Oncol.* 24:1499–1503.
 20. Tamura, T., A. Kuwahara, K. Kadoyama, M. Yamamori, K. Nishiguchi, T. Inokuma, et al. 2011. Effects of bolus injection of 5-fluorouracil on steady-state plasma concentrations of 5-fluorouracil in Japanese patients with advanced colorectal cancer. *Int. J. Med. Sci.* 8:406–412.
 21. Sobrero, A. F., C. Aschele, and J. R. Bertino. 1997. Fluorouracil in colorectal cancer—a tale of two drugs: implications for biochemical modulation. *J. Clin. Oncol.* 15:368–381.
 22. James, E. S., X. Yao, X. Cong, S. Stein, K. Kaley, C. Hahn, et al. 2014. Interim analysis of a phase II study of dose-modified FOLFIRINOX (mFOLFIRINOX) in locally advanced (LAPC) and metastatic pancreatic cancer (MPC). *ASCO Meeting Abstr.* 32(Suppl. 3): 256.
 23. Leichman, C. G., L. Leichman, C. P. Spears, P. J. Rosen, F. Muggia, S. Jeffers, et al. 1990. Biological modification of protracted infusion of 5-fluorouracil with weekly leucovorin. A dose seeking clinical trial for patients with disseminated gastrointestinal cancers. *Cancer Chemother. Pharmacol.* 26:57–61.
 24. Blazer, M. A., C. S.-Y. Wu, R. M. Goldberg, G. S. Phillips, C. R. Schmidt, P. Muscarella, et al. 2014. Tolerability and efficacy of modified FOLFIRINOX (mFOLFIRINOX) in patients with borderline-resectable pancreatic cancer (BRPC) and locally advanced unresectable pancreatic cancer (LAURPC). *ASCO Meeting Abstr.* 32(Suppl. 3): 275.
 25. Gunturu, K. S., J. R. Thumar, H. S. Hochster, S. Stein, X. Yao, X. Cong, et al. 2012. Single-institution experience with FOLFIRINOX in advanced pancreatic cancer (PC). *ASCO Meeting Abstr.* 30(Suppl. 4): 330.
 26. Alessandretti, M. B., E. P. Brandao, C. M. Abrahao, A. R. Lino, R. M. Junior, M. A. Costa, et al. 2013. Safety and efficacy of modified dose-attenuated FOLFIRINOX chemotherapy in patients over 65 years with advanced pancreatic adenocarcinoma. *ASCO Meeting Abstr.* 31 (Suppl. 15): e15176.

27. Metges, J. P., J. F. Ramee, J.-Y. Douillard, E. Boucher, R. Faroux, V. Guerin-Meyer, et al. 2014. Efficacy and safety of FOLFIRINOX in patients with metastatic pancreatic cancer. *ASCO Meeting Abstr.* 32(Suppl. 3): 305.
28. Innocenti, F., R. L. Schilsky, J. Ramirez, L. Janisch, S. Undevia, L. K. House, et al. 2014. Dose-finding and pharmacokinetic study to optimize the dosing of irinotecan according to the UGT1A1 genotype of patients with cancer. *J. Clin. Oncol.* 32:2328–2334.
29. Hosein, P. J., J. Macintyre, C. Kawamura, J. C. Maldonado, V. Ernani, A. Loaiza-Bonilla, et al. 2012. A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. *BMC Cancer* 12:199.
30. Faris, J. E., L. S. Blaszkowsky, S. McDermott, A. R. Guimaraes, J. Szyminiak, M. A. Huynh, et al. 2013. FOLFIRINOX in locally advanced pancreatic cancer: the Massachusetts General Hospital Cancer Center experience. *Oncologist* 18:543–548.
31. Morris-Stiff, G., Y. M. Tan, and J. N. Vauthey. 2008. Hepatic complications following preoperative chemotherapy with oxaliplatin or irinotecan for hepatic colorectal metastases. *Eur. J. Surg. Oncol.* 34:609–614.
32. Nomura, R., Y. Ishizaki, K. Suzuki, and S. Kawasaki. 2007. Development of hepatic steatosis after pancreatoduodenectomy. *AJR Am. J. Roentgenol.* 189:1484–1488.
33. Zorzi, D., A. Laurent, T. M. Pawlik, G. Y. Lauwers, J. N. Vauthey, and E. K. Abdalla. 2007. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. *Br. J. Surg.* 94:274–286.
34. Samuel, N., and T. J. Hudson. 2012. The molecular and cellular heterogeneity of pancreatic ductal adenocarcinoma. *Nat. Rev. Gastroenterol. Hepatol.* 9:77–87.
35. Ghosn, M., F. Farhat, J. Kattan, F. Younes, W. Moukadem, F. Nasr, et al. 2007. FOLFOX-6 combination as the first-line treatment of locally advanced and/or metastatic pancreatic cancer. *Am. J. Clin. Oncol.* 30:15–20.
36. Taieb, J., T. Lecomte, T. Aparicio, A. Asnacios, T. Mansourbakht, P. Artu, et al. 2007. FOLFIRI.3, a new regimen combining 5-fluorouracil, folinic acid and irinotecan, for advanced pancreatic cancer: results of an Association des Gastro-Enterologues Oncologues (Gastroenterologist Oncologist Association) multicenter phase II study. *Ann. Oncol.* 18:498–503.
37. Son, C. O., S. G. Pai, S. Satti, A. Dornelles, J. S. Bolton, W. C. Conway, et al. 2014. Outcomes of neoadjuvant chemotherapy with FOLFOX/FOLFIRINOX and chemoradiotherapy in borderline resectable pancreatic cancer: Single-institution experience. *ASCO Meeting Abstr.* 32(Suppl. 3): 327.
38. Oettle, H., P. Neuhaus, A. Hochhaus, J. T. Hartmann, K. Gellert, K. Ridwelski, et al. 2013. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *JAMA* 310:1473–1481.
39. Sultana, A., T. Cox, P. Ghaneh, and J. P. Neoptolemos. 2012. Adjuvant therapy for pancreatic cancer. *Recent Results Cancer Res.* 196:65–88.
40. Hardacre, J. M., M. Mulcahy, W. Small, M. Talamonti, J. Obel, S. Krishnamurthi, et al. 2013. Addition of algenpantucel-L immunotherapy to standard adjuvant therapy for pancreatic cancer: a phase 2 study. *J. Gastrointest. Surg.* 17:94–100; discussion p 00–1.
41. Weden, S., M. Klemp, I. P. Gladhaug, M. Moller, J. Eriksen, G. Gaudernack, et al. 2011. Long-term follow-up of patients with resected pancreatic cancer following vaccination against mutant K-ras. *Int. J. Cancer* 128:1120–1128.
42. Haeno, H., M. Gonen, M. B. Davis, J. M. Herman, C. A. Iacobuzio-Donahue, and F. Michor. 2012. Computational modeling of pancreatic cancer reveals kinetics of metastasis suggesting optimum treatment strategies. *Cell* 148:362–375.
43. Tuveson, D. A., and J. P. Neoptolemos. 2012. Understanding metastasis in pancreatic cancer: a call for new clinical approaches. *Cell* 148:21–23.
44. Sohal, D. P., R. M. Walsh, R. K. Ramanathan, and A. A. Khorana. 2014. Pancreatic adenocarcinoma: treating a systemic disease with systemic therapy. *J. Natl. Cancer Inst.* 106: dju011.
45. Evans, D. B., G. R. Varadhachary, C. H. Crane, C. C. Sun, J. E. Lee, P. W. Pisters, et al. 2008. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. *J. Clin. Oncol.* 26:3496–3502.
46. MacKenzie, S., H. Zeh, L. E. McCahill, T. D. Sielaff, N. Bahary, T. E. Gribben, et al. 2013. A pilot phase II multicenter study of nab-paclitaxel (Nab-P) and gemcitabine (G) as preoperative therapy for potentially resectable pancreatic cancer (PC). *ASCO Meeting Abstr.* 31 (Suppl. 15): 4038.
47. Alvarez-Gallego, R., A. Cubillo, J. Rodriguez-Pascual, Y. Quijano, E. De Vicente, L. Garcia, et al. 2012. Antitumor activity of nab-paclitaxel and gemcitabine in resectable pancreatic cancer. *ASCO Meeting Abstr.* 30(Suppl. 15): 4040.
48. Minter, R. M., M. U.-S. Feng, M. Al-Hawary, J. Shen, M. J. Schipper, F. Bednar, et al. 2014. Effect of neoadjuvant chemoradiotherapy (nCRT) on survival in patients with borderline resectable (BR) pancreatic adenocarcinoma (PDA) with acceptable peri-operative morbidity. *ASCO Meeting Abstr.* 32(Suppl. 3): 288.
49. McCormick, K., S. H. Whiting, G. Gyurkey, W.-J. Koh, M. Sinanan, and A. L. Coveler. 2014. Long-term survival of patients receiving multimodality neoadjuvant therapy for resectable or borderline resectable pancreatic ductal adenocarcinoma. *ASCO Meeting Abstr.* 32(Suppl. 3): 309.
50. Gulati, A. P., S. M. Schreiber, B. Schrope, J. A. Lee, J. Allendorf, J. A. Chabot, et al. 2014. Prospective phase II

- study of inoperable pancreatic adenocarcinoma with neoadjuvant gemcitabine, docetaxel, and capecitabine (GTX). ASCO Meeting Abstr. 32(Suppl. 3): 274.
51. Christians, K. K., S. Tsai, A. Mahmoud, P. Ritch, J. P. Thomas, L. Wiebe, et al. 2014. Neoadjuvant FOLFIRINOX for borderline resectable pancreas cancer: a new treatment paradigm? *Oncologist* 19:266–274.
 52. Tian, F., H. E. Appert, J. Myles, and J. M. Howard. 1992. Prognostic value of serum CA 19-9 levels in pancreatic adenocarcinoma. *Ann. Surg.* 215:350–355.
 53. Haglund, C., P. Kuusela, and P. J. Roberts. 1989. Tumour markers in pancreatic cancer. *Ann. Chir. Gynaecol.* 78:41–53.
 54. Benhamou, P. Y., J. P. Vuillez, S. Halimi, G. Meffre, and I. Bachelot. 1991. Influence of metabolic disturbances of diabetes mellitus on serum CA 19-9 tumor marker. *Diabete Metab.* 17:39–43.
 55. Pelzer, U., A. Hilbig, M. Sinn, J. Stieler, M. Bahra, B. Dorken, et al. 2013. Value of carbohydrate antigen 19-9 in predicting response and therapy control in patients with metastatic pancreatic cancer undergoing first-line therapy. *Front. Oncol.* 3:155.
 56. Von Hoff, D. D., T. Ervin, F. P. Arena, E. G. Chiorean, J. Infante, M. Moore, et al. 2013. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N. Engl. J. Med.* 369:1691–1703.
 57. Hess, V., B. Glimelius, P. Grawe, D. Dietrich, G. Bodoky, T. Ruhstaller, et al. 2008. CA 19-9 tumour-marker response to chemotherapy in patients with advanced pancreatic cancer enrolled in a randomised controlled trial. *Lancet Oncol.* 9:132–138.
 58. Donahue, T. R., W. H. Isacoff, O. J. Hines, J. S. Tomlinson, J. J. Farrell, Y. M. Bhat, et al. 2011. Downstaging chemotherapy and alteration in the classic computed tomography/magnetic resonance imaging signs of vascular involvement in patients with pancreaticobiliary malignant tumors: influence on patient selection for surgery. *Arch. Surg.* 146:836–843.
 59. Katz, M. H., J. B. Fleming, P. Bhosale, G. Varadhachary, J. E. Lee, R. Wolff, et al. 2012. Response of borderline resectable pancreatic cancer to neoadjuvant therapy is not reflected by radiographic indicators. *Cancer* 118:5749–5756.
 60. Dholakia, H.-P., and R. Wild. 2013. Resection of borderline resectable pancreatic cancer after neoadjuvant chemoradiation does not depend on improved radiographic appearance of tumor–vessel relationships. *J. Radiat. Oncol.* 2:413–425.
 61. Zhao, Q., A. Rashid, Y. Gong, and M. Katz. 2012. Pathologic complete response to neoadjuvant therapy in patients with pancreatic ductal adenocarcinoma is associated with a better prognosis. *Ann. Diagn. Pathol.* 16:29–37.
 62. Chun, Y. S. C. H., S. J. Cohen, A. Konski, B. Burtress, C. S. Denlinger, I. Astsaturov, et al. 2011. Significance of pathologic response to preoperative therapy in pancreatic cancer. *Ann. Surg. Oncol.* 18:3601–3607.
 63. De Angelis, C., R. F. Brizzi, and R. Pellicano. 2013. Endoscopic ultrasonography for pancreatic cancer: current and future perspectives. *J. Gastrointest. Oncol.* 4:220–230.
 64. Lu, N., X. Y. Feng, S. J. Hao, Z. H. Liang, C. Jin, J. W. Qiang, et al. 2011. 64-slice CT perfusion imaging of pancreatic adenocarcinoma and mass-forming chronic pancreatitis. *Acad. Radiol.* 18:81–88.
 65. Epelbaum, R., O. Israel, R. Haddad, N. Sikorski, and A. Frenkel. 2010. Dynamic FDG-PET/CT as an indicator of tumor aggressiveness and patient outcome in pancreatic cancer. ASCO Meeting Abstr. 28(Suppl. 15): e14526.
 66. Koay, E. J., M. J. Truty, V. Cristini, R. M. Thomas, R. Chen, D. Chatterjee, et al. 2014. Transport properties of pancreatic cancer describe gemcitabine delivery and response. *J. Clin. Invest.* 124:1525–1536.
 67. Hammel, P., F. Huguet, J.-L. Van Laethem, D. Goldstein, B. Glimelius, P. Artru, et al. 2013. Comparison of chemoradiotherapy (CRT) and chemotherapy (CT) in patients with a locally advanced pancreatic cancer (LAPC) controlled after 4 months of gemcitabine with or without erlotinib: final results of the international phase III LAP 07 study. ASCO Meeting Abstr. 31(Suppl. 15): LBA4003.
 68. Chuong, M. D., G. M. Springett, J. M. Freilich, C. K. Park, J. M. Weber, E. A. Mellon, et al. 2013. Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated. *Int. J. Radiat. Oncol. Biol. Phys.* 86:516–522.
 69. Chang, S. T., K. A. Goodman, G. P. Yang, and A. C. Koong. 2007. Stereotactic body radiotherapy for unresectable pancreatic cancer. *Front. Radiat. Ther. Oncol.* 40:386–394.
 70. Ramanathan, R. K., P. Lee, J. E. Seng, S. P. Anthony, P. J. Rosen, R. R. Mena, et al. 2014. Phase II study of induction therapy with gemcitabine and nab-paclitaxel followed by consolidation with mFOLFIRINOX in patients with metastatic pancreatic cancer. ASCO Meeting Abstr. 32 (Suppl. 3): 224.
 71. Hartlapp, I., J. Muller, W. Kenn, U. Steger, C. Isbert, M. Schuerlen, et al. 2013. Complete pathological remission of locally advanced, unresectable pancreatic cancer (LAPC) after intensified neoadjuvant chemotherapy. *Onkologie* 36:123–125.
 72. Zhang, Y., H. S. Hochster, S. Stein, and J. Lacy. 2014. Second-line gemcitabine plus nab-paclitaxel (G+A) for advanced pancreatic cancer (APC) after first-line FOLFIRINOX: single institution retrospective review of efficacy and toxicity. ASCO Meeting Abstr. 32(Suppl. 3): 344.
 73. Spivak-Kroizman, T. R., G. Hostetter, R. Posner, M. Aziz, C. Hu, M. J. Demeure, et al. 2013. Hypoxia triggers hedgehog-mediated tumor-stromal interactions in pancreatic cancer. *Cancer Res.* 73:3235–3247.

74. Sonnenblick, A., L. Kadouri, L. Appelbaum, T. Peretz, M. Sagi, Y. Goldberg, et al. 2011. Complete remission, in BRCA2 mutation carrier with metastatic pancreatic adenocarcinoma, treated with cisplatin based therapy. *Cancer Biol. Ther.* 12:165–168.
75. Leung, K., and M. W. Saif. 2013. BRCA-associated pancreatic cancer: the evolving management. *J. Pancreas* 14:149–151.
76. Jones, S., X. Zhang, D. W. Parsons, J. C. Lin, R. J. Leary, P. Angenendt, et al. 2008. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. *Science* 321:1801–1806.
77. Reed, E. 2005. ERCC1 and clinical resistance to platinum-based therapy. *Clin. Cancer Res.* 11:6100–6102.
78. Hu, Y. C., R. A. Komorowski, S. Graewin, G. Hostetter, O. P. Kallioniemi, H. A. Pitt, et al. 2003. Thymidylate synthase expression predicts the response to 5-fluorouracil-based adjuvant therapy in pancreatic cancer. *Clin. Cancer Res.* 9:4165–4171.
79. Spratlin, J., R. Sangha, D. Glubrecht, L. Dabbagh, J. D. Young, C. Dumontet, et al. 2004. The absence of human equilibrative nucleoside transporter 1 is associated with reduced survival in patients with gemcitabine-treated pancreas adenocarcinoma. *Clin. Cancer Res.* 10:6956–6961.
80. Poplin, E., H. Wasan, L. Rolfe, M. Raponi, T. Ik Dahl, I. Bondarenko, et al. 2013. Randomized, multicenter, phase II study of CO-101 versus gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma: including a prospective evaluation of the role of hENT1 in gemcitabine or CO-101 sensitivity. *J. Clin. Oncol.* 31:4453–4461.
81. Von Hoff, D. D., R. Ramanathan, M. Borad, D. Laheru, L. Smith, T. Wood, et al. 2009. SPARC correlation with response to gemcitabine (G) plus nab-paclitaxel (nab-P) in patients with advanced metastatic pancreatic cancer: a phase I/II study. *ASCO Meeting Abstr.* 27:4525.
82. Sinn, M., B. V. Sinn, J. K. Striefler, J. L. Lindner, J. M. Stieler, P. Lohneis, et al. 2014. SPARC expression in resected pancreatic cancer patients treated with gemcitabine: results from the CONKO-001 study. *Ann. Oncol.* 25:1025–1032.
83. Arnaoutakis, G. J., D. Rangachari, D. A. Laheru, C. A. Jacobuzio-Donahue, R. H. Hruban, J. M. Herman, et al. 2011. Pulmonary resection for isolated pancreatic adenocarcinoma metastasis: an analysis of outcomes and survival. *J. Gastrointest. Surg.* 15:1611–1617.
84. Dunschede, F., L. Will, C. von Langsdorf, M. Mohler, P. R. Galle, G. Otto, et al. 2010. Treatment of metachronous and simultaneous liver metastases of pancreatic cancer. *Eur. Surg. Res.* 44:209–213.

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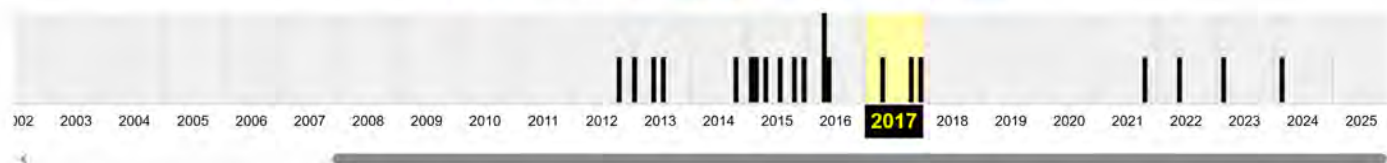
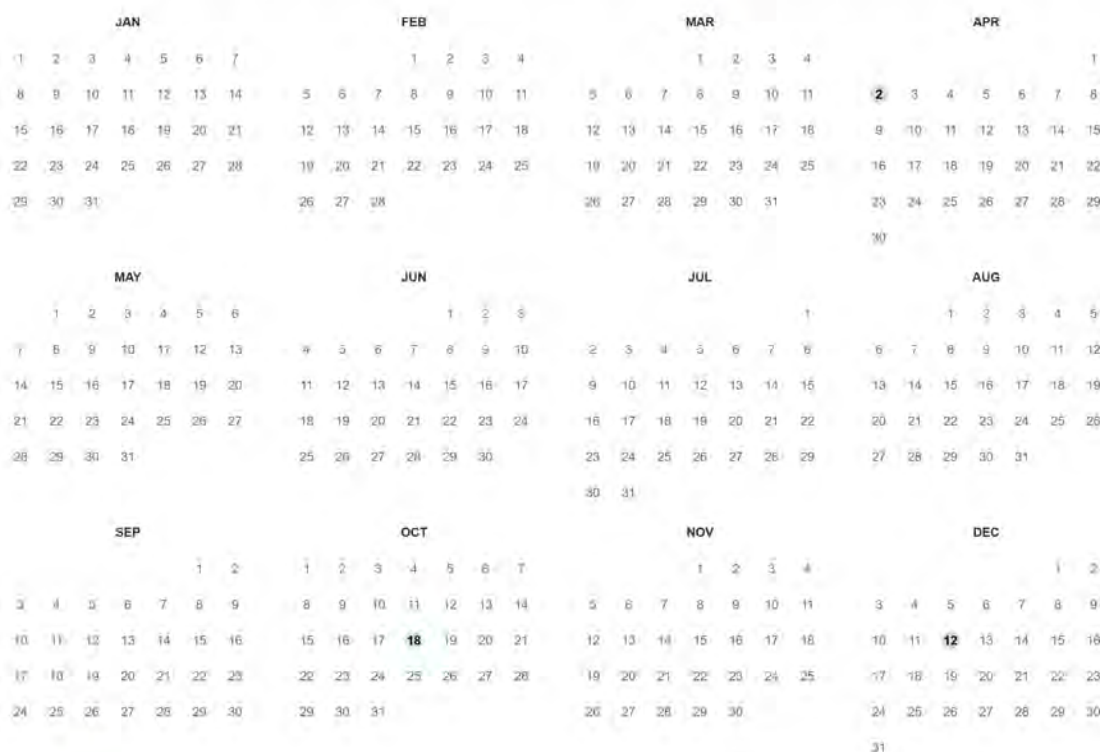
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V.1.2010	日本語版	英語版	コメント	【監訳・監修】 内藤誠二/荒井陽一 【監訳】 平尾佳彦/田中宣道

●精巣がん Testicular Cancer

V.2.2015	日本語版	英語版	コメント	【監訳・監修】 内藤誠二 【監訳】 三木恒治/中村晃和
V.1.2012	日本語版	英語版	コメント	【監訳・監修】 本間之夫/窪田吉信 【監訳】 三木恒治/中村晃和
V.2.2011	日本語版	英語版	コメント	【監訳・監修】 本間之夫/窪田吉信 【監訳】 三木恒治/中村晃和
V.2.2010	日本語版	英語版	コメント	【監訳・監修】 内藤誠二/荒井陽一 【監訳】 三木恒治/中村晃和

●陰茎がん Testicular Cancer

V.1.2014	日本語版	英語版	コメント	【監訳・監修】 内藤誠二 【監訳】 小川良雄/富士幸藏
V.1.2012	日本語版	英語版	コメント	【監訳・監修】 本間之夫/窪田吉信 【監訳】 小川良雄/富士幸藏

●前立腺がんの早期発見 Prostate Cancer Early Detection

V.1.2014	日本語版	英語版	コメント	【監訳・監修】 内藤誠二 【監訳】 鈴木和浩/伊藤一人
V.2.2012	日本語版	英語版	コメント	【監訳・監修】 本間之夫/窪田吉信 【監訳】 鈴木和浩/伊藤一人
V.1.2011	日本語版	英語版	コメント	【監訳・監修】 本間之夫/窪田吉信 【監訳】 鈴木和浩/伊藤一人
V.2.2010	日本語版	英語版	コメント	【監訳・監修】 内藤誠二/荒井陽一 【監訳】 鈴木和浩/伊藤一人/ 眞 善行/赤塚英之/ 額川 晋/古賀寛史/舩森直哉/赤倉功一郎/ 川島清隆/沖原宏治

肺がん

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●小細胞肺がん Small Cell Lung Cancer

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V.1.2010	日本語版	英語版	コメント	【監訳責任】 一瀬 幸人/中西 洋一 【監訳】 田村 友秀/井内 康輝/多田 弘人/池田 徳彦/ 上岡 博/奥屋 朝幸/中川 和彦/早川 和重/ 光富 徹哉/吉野 一郎

●非小細胞肺がん Non-Small Cell Lung Cancer

V.2.2013	日本語版	英語版	コメント	【監訳責任】 中西 洋一 【監訳】 薬物療法及び集学的治療小委員会 委員長 山本 信之 副委員長 武田 寛司 委員 朝比奈 肇/石川 仁/井上 彰/白田 実男/ 倉田 宏保/弦間 紀彦/後藤 功一/近藤 征史/ 里内美弥子/関 嗣彦/瀬戸 貴司/坪井 正博/ 中村 洋一/中山 優子/野上 尚之/原田 英幸/ 堀田 樹幸/村上 晴泰/山本 昇 外科療法小委員会 委員長 一瀬 幸人 副委員長 岡田 守人 委員 大奥 弘幸/鈴木 健司/竹之山 光広 放射線治療小委員会 委員長 早川 和重 副委員長 石川 仁/江原 威/沖本 智昭/唐澤 克之/ 委員 塩山 雅之/辻谷 景子/永田 靖/西村 恭昌/ 野中 哲生/原田 英幸
V.2.2012	日本語版	英語版	コメント	【監訳責任】 中西 洋一 【監訳】 田村 友秀/永井 完治/多田 弘人/池田 徳彦/ 上岡 博/奥屋 朝幸/中川 和彦/早川 和重/ 光富 徹哉/吉野 一郎
V.2.2010	日本語版	英語版	コメント	【監訳責任】 一瀬 幸人/中西 洋一 【監訳】 田村 友秀/井内 康輝/多田 弘人/池田 徳彦/ 上岡 博/奥屋 朝幸/中川 和彦/早川 和重/ 光富 徹哉/吉野 一郎

●悪性胸膜中皮腫 Malignant Pleural Mesothelioma

V.1.2014	日本語版	英語版	コメント	【監訳責任】 中西 洋一 【監訳】 胸膜中皮腫小委員会 委員長 中野 孝司 副委員長 長谷川 誠紀 委員 石川 雄一/岡田 守人/金子 公一/ 川真田 修/木村 智樹/辻谷 景子/ 関戸 好孝/高橋 和久/田中文啓/ 永安 武/中山 優子/廣嶋 健三/ 横井 香平
V.2.2012	日本語版	英語版	コメント	【監訳責任】 中西 洋一 【監訳】 中野 孝司

●胸腺腫および胸腺がん Thymomas and Thymic Carcinomas

V.1.2014	日本語版	英語版	コメント	【監訳責任】 中西 洋一 【監訳】 胸腺腫瘍小委員会 委員長 奥村明之進 副委員長 近藤 和也 委員 内海 朝香/門田 嘉久/國崎 英夫/ 辻谷 景子/清水 重喜/土田 正則/ 原 眞咲/深井 一郎/村川 知弘/ 山崎 直哉
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V.2.2012	日本語版	英語版	コメント	【監訳責任】中西 洋一 【監訳】 奥村 明之進
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婦人科がん

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子宮頸がん Cervical Cancer

V.1.2016	日本語版	英語版	コメント	【監訳・監修】片岡秀隆 / 小宮山慎一 【監訳】 斎藤 泰 / 岩崎雅宏
V.1.2015	日本語版	英語版	コメント	【監訳・監修】片岡秀隆 / 小宮山慎一 【監訳】 斎藤 泰 / 岩崎雅宏
V.2.2013	日本語版	英語版	コメント	【監訳・監修】嘉村敬治 / 八重樫伸生 【監訳】 斎藤 泰 / 岩崎雅宏
V.1.2011	日本語版	英語版	コメント	【監訳・監修】宇田川康博 / 八重樫伸生 【監訳】 斎藤 泰 / 岩崎雅宏

子宮体がん Uterine Neoplasms

V.2.2016	日本語版	英語版	コメント	【監訳・監修】片岡秀隆 / 小宮山慎一 【監訳】 永瀬 智 / 須藤 毅
V.1.2014	日本語版	英語版	コメント	【監訳・監修】片岡秀隆 / 小宮山慎一 【監訳】 八重樫伸生 / 永瀬 智
V.3.2012	日本語版	英語版	コメント	【監訳・監修】嘉村敬治 / 八重樫伸生 【監訳】 八重樫伸生 / 永瀬 智
V.2.2011	日本語版	英語版	コメント	【監訳・監修】宇田川康博 / 八重樫伸生 【監訳】 八重樫伸生 / 永瀬 智

卵巣がん Ovarian Cancer

V.2.2015	日本語版	英語版	コメント	【監訳・監修】片岡秀隆 / 小宮山慎一 【監訳】 紀川純三 / 板持広明
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V.2.2011	日本語版	英語版	コメント	【監訳・監修】宇田川康博 / 八重樫伸生 【監訳】 紀川純三 / 板持広明

子宮頸がんスクリーニング Cervical Cancer Screening

V.2.2012	日本語版	英語版	コメント	【監訳・監修】嘉村敬治 / 八重樫伸生 【監訳】 片岡秀隆 / 田代浩徳
V.1.2011	日本語版	英語版	コメント	【監訳・監修】宇田川康博 / 八重樫伸生 【監訳】 片岡秀隆 / 田代浩徳

乳がんおよび卵巣がんにおける遺伝的/家族性リスク評価

Genetic/Familial High-Risk Assessment: Breast and Ovarian

V.2.2015	日本語版	英語版	コメント	【監訳・監修】片岡秀隆 / 小宮山慎一、中村清吾* / 向井博文* 【監訳】 青木大輔 / 平沢晃、平成人* / 河合賢朗*
V.1.2012	日本語版	英語版	コメント	【監訳・監修】嘉村敬治 / 八重樫伸生 【監訳】 青木大輔 / 平沢晃、中村清吾*
V.1.2011	日本語版	英語版	コメント	【監訳・監修】宇田川康博 / 八重樫伸生 【監訳】 青木大輔 / 平沢晃、中村清吾*

*日本乳癌学会

膵臓がん

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膵臓がん Pancreatic Adenocarcinoma

V.2.2015	日本語版	英語版	コメント	【監訳・責任】山口幸二
V.1.2013	日本語版	英語版	コメント	【監訳・責任】山口幸二 【監訳】 佐藤典宏 / 森泰寿
V.1.2012	日本語版	英語版	コメント	【監訳・責任】山口幸二 【監訳】 佐藤典宏 / 森泰寿

原発不明がん

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原発不明がん Occult Primary (Cancer of Unknown Primary) [CUP]

V.1.2015	日本語版	英語版	コメント	【監訳・責任】倉田 宝保 【監訳】 倉田 宝保 / 安藤 正志 / 安井 久晃
V.1.2013	日本語版	英語版	コメント	【監訳・責任】向井 博文 【監訳】 倉田 宝保 / 松原 伸晃 / 向井 博文 / 安井 久晃
V.1.2012	日本語版	英語版	コメント	【監訳・責任】室 圭 / 向井 博文 【監訳】 倉田 宝保 / 松原 伸晃 / 向井 博文 / 安井 久晃

乳がん

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乳がん Breast Cancer

V.3.2015	日本語版	英語版	コメント	【監訳・監修】 中村清吾 / 向井博文 【監訳】 外科療法: 神野浩光 / 服部正也 放射線療法: 山内智香子 / 白石憲史郎 薬物療法: 相原智彦 / 相良安昭 病理: 堀井理絵 / 堀口 一 郎
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乳がん リスク低減 Breast Cancer Risk Reduction

V.2.2015	日本語版	英語版	コメント	【監訳・監修】中村清吾 / 向井博文 【監訳】平成人 / 河合賢朗
----------	------	-----	------	--------------------------------------

乳がんおよび卵巣がんにおける遺伝的/家族性リスク評価

Genetic/Familial High-Risk Assessment: Breast and Ovarian

V.2.2015	日本語版	英語版	コメント	【監訳・監修】中村清吾 / 向井博文、片岡秀隆* / 小宮山慎一* 【監訳】平成人 / 河合賢朗、青木大輔* / 平沢晃*
V.1.2012	日本語版	英語版	コメント	【監訳・監修】嘉村敬治* / 八重樫伸生* 【監訳】青木大輔* / 平沢晃*、中村清吾
V.1.2011	日本語版	英語版	コメント	【監訳・監修】宇田川康博* / 八重樫伸生* 【監訳】青木大輔* / 平沢晃*、中村清吾

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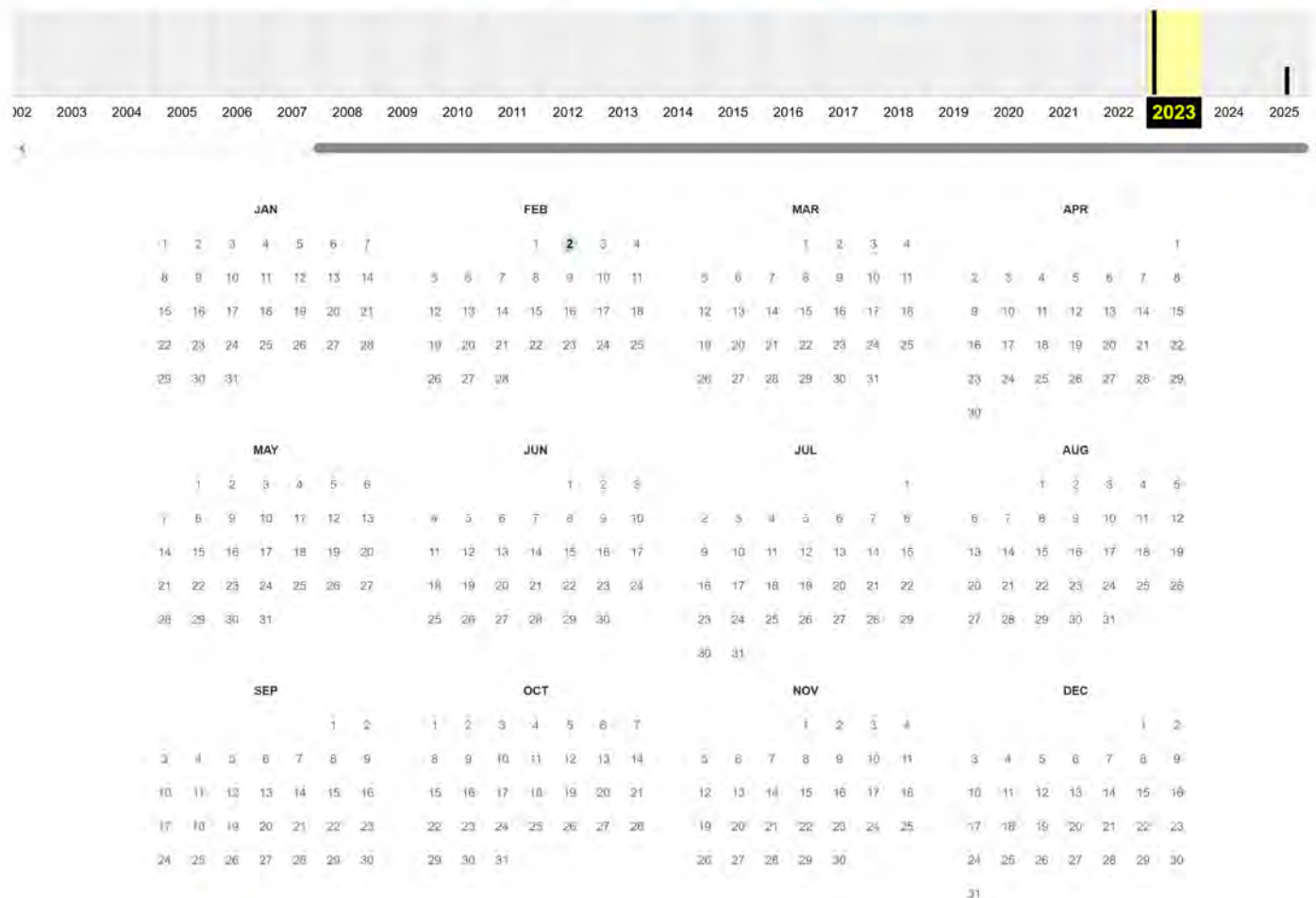
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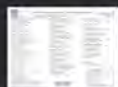
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Pancreatic Adenocarcinoma

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Dana-Farber/Brigham and Women's
Cancer Center

NCCN

Jennifer Burns
Deborah Freedman-Cass, PhD

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¶ Surgery/surgical oncology
§ Radiotherapy/radiation oncology
† Medical oncology
‡ Hematology/hematology oncology
P Internal medicine
~ Interventional radiology
≠ Pathology
¥ Patient advocacy
* Writing Committee Member

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Pancreatic Adenocarcinoma Panel: Imaging Subcommittee

NCCN gratefully acknowledges the following subcommittee members for their contributions during the update of the Principles of Diagnosis, Imaging and Staging (PANC-A) and Criteria Defining Resectability Status (PANC-B) in Version 1.2015 of the NCCN Guidelines for Pancreatic Adenocarcinoma:

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Cancer Center

Eric Tamm, MD ϕ
The University of Texas
MD Anderson Cancer Center

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 ϕ Diagnostic radiology

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[Clinical Suspicion of Pancreatic Cancer or
Evidence of Dilated Pancreatic and/or Bile Duct \(PANC-1\)](#)

[No Metastatic Disease on Physical Exam and by Imaging \(PANC-2\)](#)

[Resectable, Workup, Treatment \(PANC-3\)](#)

[Borderline Resectable, No Metastases, Planned Neoadjuvant Therapy \(PANC-4\)](#)

[Borderline Resectable, No Metastases, Planned Resection \(PANC-5\)](#)

[Postoperative Adjuvant Treatment \(PANC-6\)](#)

[Locally Advanced, Unresectable \(PANC-7\)](#)

[Metastatic Disease \(PANC-9\)](#)

[Recurrence After Resection \(PANC-10\)](#)

[Principles of Diagnosis, Imaging, and Staging \(PANC-A\)](#)

[Criteria Defining Resectability Status \(PANC-B\)](#)

[Principles of Surgical Technique \(PANC-C\)](#)

[Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting \(PANC-D\)](#)

[Principles of Palliation and Supportive Care \(PANC-E\)](#)

[Principles of Radiation Therapy \(PANC-F\)](#)

[Principles of Chemotherapy \(PANC-G\)](#)

[American Joint Committee on Cancer \(AJCC\) TNM Staging of Pancreatic Cancer \(2010\) \(ST-1\)](#)

Clinical Trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, [click here: nccn.org/clinical_trials/physician.html](#).

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See [NCCN Categories of Evidence and Consensus](#).

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Updates in Version 2.2015 of the NCCN Guidelines for Pancreatic Adenocarcinoma from Version 1.2015 include:

PANC-3

- Recommendations were clarified for the use of celiac plexus neurolysis when cancer is found to be unresectable at surgery: "... ± celiac plexus neurolysis if pain when indicated by pain (category 2B if no pain)." (Also for PANC-4 and PANC-5)

Updates in Version 1.2015 of the NCCN Guidelines for Pancreatic Adenocarcinoma from Version 2.2014 include:

General

- "Duodenal bypass" was changed to "gastrojejunostomy" throughout.
- "Open celiac plexus block" was changed to "celiac plexus neurolysis" throughout.
- "Short metal stent" and "stent" were changed to "self-expanding metal stent" throughout.
- "Salvage therapy" was changed to "second-line therapy" throughout.

Introduction

- The introduction statement was clarified: "...at a high-volume center with reference to use of appropriate imaging studies."

PANC-1

- Under workup, MRI was removed: "Pancreatic protocol CT or MRI (See PANC-A)."
- No mass in pancreas on imaging, no metastatic disease: EUS is now listed as a separate and "preferred" option over MRCP or ERCP.

PANC-2

- Footnote "g" was added: "Self-expanding metal stent as clinically indicated in patients with select comorbidities or when surgery may be delayed. (See Discussion)."

PANC-3

- Footnote "i" was revised: "There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. *Acceptable regimens include FOLFIRINOX or gemcitabine + albumin-bound paclitaxel. Subsequent chemoradiation is sometimes included.* Most NCCN Member Institutions prefer neoadjuvant therapy at a high-volume center." (Also on PANC-4)

PANC-6

- Footnote "m" was revised: "... Adjuvant treatment should be administered to patients who have not had neoadjuvant chemotherapy and who have adequately recovered from surgery; treatment should be initiated within 4- 8 12 weeks...."

PANC-8

- Under treatment, "fluoropyrimidine + oxaliplatin (category 2B)" was added for consistency with the acceptable chemotherapy combinations listed on PANC-G (1 of 3) for patients with good performance status and locally advanced or metastatic disease. (Also on PANC-9)
- Footnote "u" was revised: "Based on preliminary data from the LAP-07 trial, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy. *Chemoradiation may improve local control and delay the need for resumption therapy.* (Huguet F, Hammel P, Vernerey D, et al. *Impact of chemoradiation on local control and time without treatment in patients with locally advanced pancreatic cancer included in the international phase III LAP 07 study.* J Clin Oncol 2014; 32:5s. Abstract 4001.) (Also for footnote "a" on PANC-F 2 of 6)

PANC-9

- For good performance status, the treatment options were separated into two groups, "Preferred" and "Other options." Preferred options are: "Clinical trial, or FOLFIRINOX (category 1), or Gemcitabine + albumin-bound paclitaxel (category 1)."

PANC-10

- Footnote "z" was added: "For more information about the treatment of isolated pulmonary metastases, see Discussion."

[Continued on next page](#)

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Updates in Version 1.2015 of the NCCN Guidelines for Pancreatic Adenocarcinoma from Version 2.2014 include:

PANC-A

- This section was significantly revised and expanded.

PANC-B

- This section was significantly revised and put into table format.

PANC-E

- Gastric outlet obstruction, under poor performance status the second sub-bullet was revised: “*Venting percutaneous endoscopic gastrostomy (PEG) tube for gastric decompression.*”
- Fifth bullet was revised: “Pancreatic exocrine insufficiency (~~inadequate production of digestive enzymes~~).”

PANC-F (2 of 6)

- Under adjuvant therapy, the 3rd sub-bullet was revised: “Gemcitabine or bolus 5-FU/leucovorin or *continuous infusion 5-FU.*”

PANC-F (3 of 6)

- Fourth bullet was revised: “IORT is delivered...The role of IORT for ~~unresectable and resectable cases~~ is controversial and should only be performed at specialized centers in ~~well selected cases~~. It is *sometimes* ~~ideally~~ used in cases where surgical resection may result in close or involved margins.

PANC-G (1 of 3)

- Under Metastatic, the last bullet was revised: “Second-line chemotherapy may consist of gemcitabine-based therapy for those previously treated with fluoropyrimidine-based therapy, and fluoropyrimidine-based therapy for those previously treated with gemcitabine-based therapy. ~~Results of the CONKO-003 trial demonstrated a significant improvement in overall survival with the addition of oxaliplatin to 5-FU/leucovorin.~~”

PANC- G (2 of 3)

- Under Adjuvant, the last bullet was revised: “For patients with *good performance status* who relapse after receiving adjuvant therapy, *FOLFIRINOX or gemcitabine + albumin-bound paclitaxel are options depending on the length of time since completion of adjuvant therapy. Subsequent therapy may consist of gemcitabine or gemcitabine-based combination therapy for patients previously treated with fluoropyrimidine-based therapy, or fluoropyrimidine-based therapy (eg, 5-FU/leucovorin/oxaliplatin⁷ or CapeOx)⁸ for patients previously treated with gemcitabine-based therapy.*”
- Neoadjuvant bullet was revised: “*There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. Acceptable regimens include FOLFIRINOX or gemcitabine + albumin-bound paclitaxel. Subsequent chemoradiation is sometimes included. Most NCCN Member Institutions prefer neoadjuvant therapy at a high-volume center. Although there is insufficient evidence to recommend specific neoadjuvant regimens, most published neoadjuvant studies that were done prior to the introduction of more effective combination chemotherapy incorporated chemoradiation. Studies of these more effective regimens (ie, FOLFIRINOX or gemcitabine and albumin-bound paclitaxel) without chemoradiation are in progress.*”

MS-1

- The Discussion section was updated to reflect the changes in the algorithm.

Note: All recommendations are category 2A unless otherwise indicated.

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INTRODUCTION

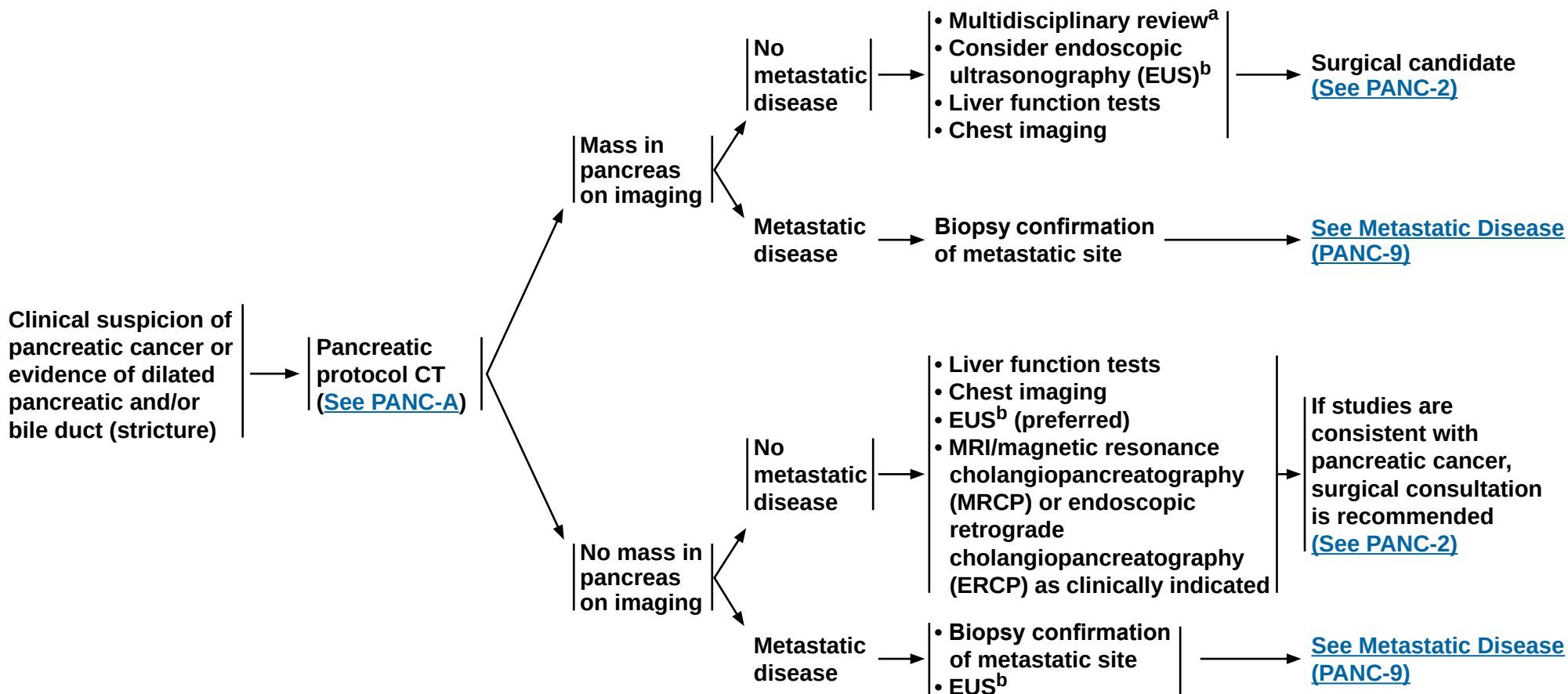
Decisions about diagnostic management and resectability should involve multidisciplinary consultation at a high-volume center with use of appropriate imaging studies.

Note: All recommendations are category 2A unless otherwise indicated.

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**CLINICAL
PRESENTATION**

WORKUP



^aMultidisciplinary review should ideally involve expertise from diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, surgery, and pathology.

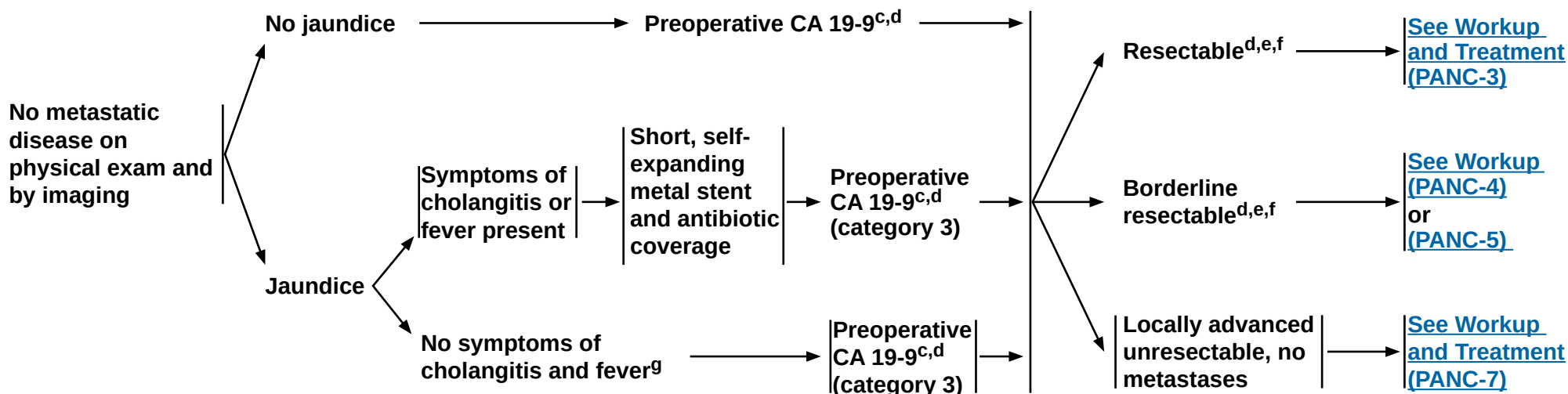
^bEUS-FNA if clinically indicated.

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CLINICAL PRESENTATION

WORKUP



^cElevated CA 19-9 does not necessarily indicate cancer or advanced disease. CA 19-9 may be elevated as a result of biliary infection (cholangitis), inflammation, or obstruction, benign or malignant. In addition, CA 19-9 may be undetectable in Lewis antigen-negative individuals. ([See Discussion](#))

^d[See Principles of Diagnosis, Imaging, and Staging \(PANC-A\)](#).

^e[See Criteria Defining Resectability Status \(PANC-B\)](#).

^f[See Principles of Surgical Technique \(PANC-C\)](#) and [Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting \(PANC-D\)](#).

^gSelf-expanding metal stent as clinically indicated in patients with select comorbidities or when surgery may be delayed. ([See Discussion](#))

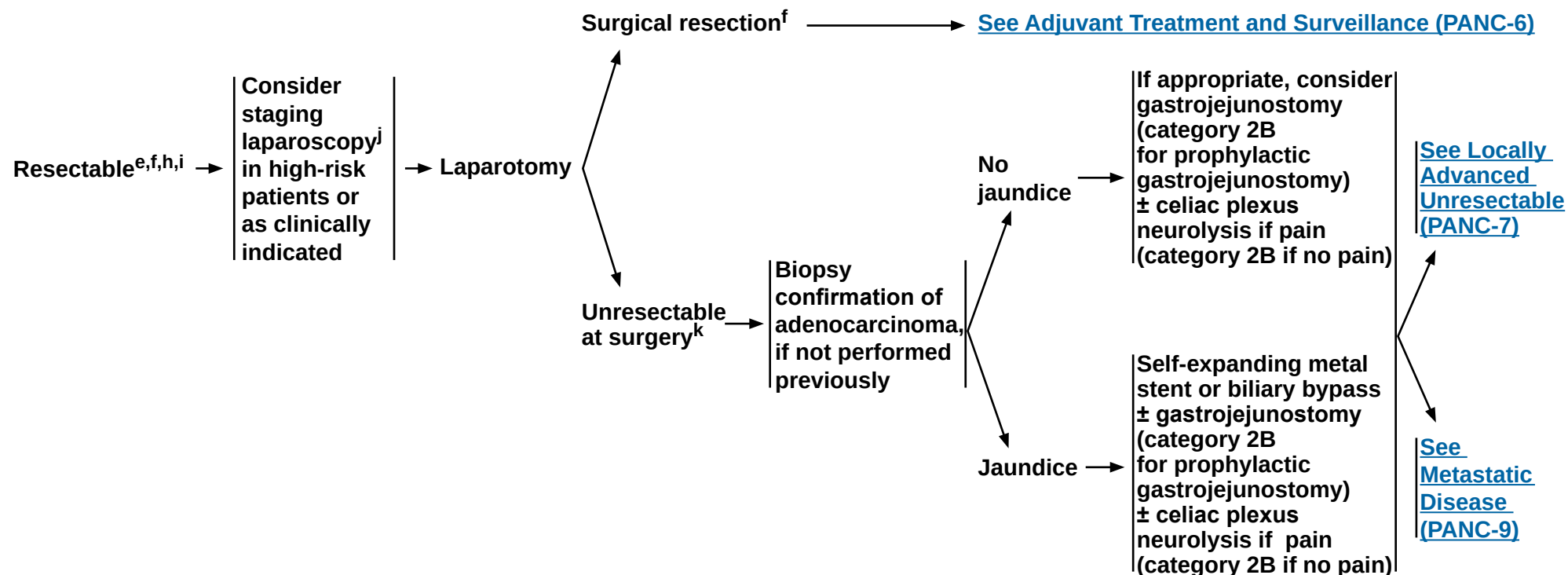
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RESECTABLE

WORKUP

TREATMENT



^eSee [Criteria Defining Resectability Status \(PANC-B\)](#).

^fSee [Principles of Surgical Technique \(PANC-C\)](#) and [Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting \(PANC-D\)](#).

^hIn selected patients who appear technically resectable but have poor prognostic features (ie, very highly elevated CA 19-9, large primary tumors, large regional lymph nodes, excessive weight loss, or extreme pain) consider neoadjuvant therapy (clinical trial preferred), which requires biopsy confirmation of adenocarcinoma ([see PANC-4](#)). For patients with biliary obstruction, durable biliary decompression is required.

ⁱThere is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. Acceptable regimens include FOLFIRINOX or gemcitabine + albumin-bound paclitaxel. Subsequent chemoradiation is sometimes included. Most NCCN Member Institutions prefer neoadjuvant therapy at a high-volume center. Performing surgery with a high likelihood of a positive margin is not recommended.

^jSee [Principles of Diagnosis, Imaging, and Staging #8 \(PANC-A\)](#).

^kSee [Principles of Palliation and Supportive Care \(PANC-E\)](#).

Note: All recommendations are category 2A unless otherwise indicated.

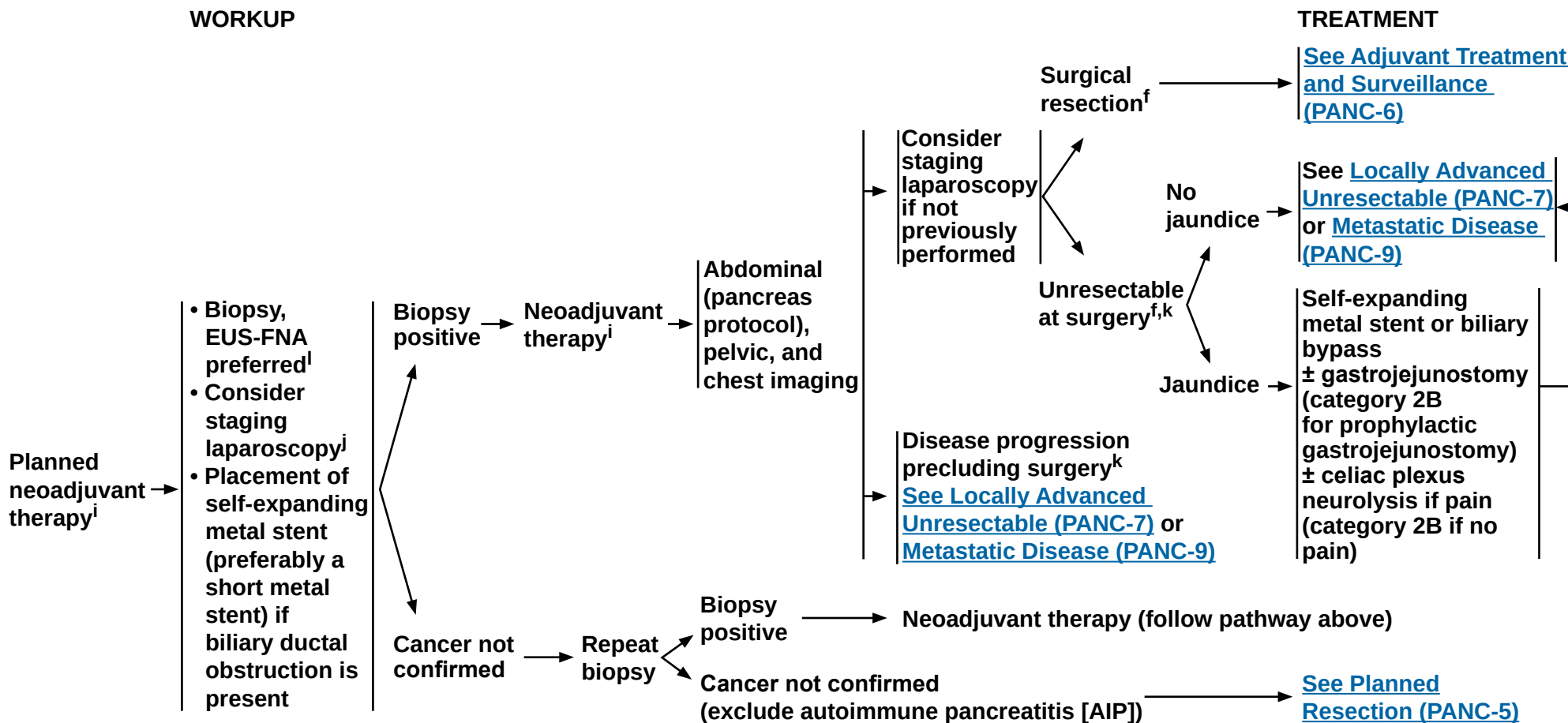
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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Pancreatic Adenocarcinoma

BORDERLINE RESECTABLE^{d,e} NO METASTASES, PLANNED NEOADJUVANT THERAPY

WORKUP



^dSee Principles of Diagnosis, Imaging, and Staging (PANC-A).

^eSee Criteria Defining Resectability Status (PANC-B).

^fSee Principles of Surgical Technique (PANC-C) and Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting (PANC-D).

ⁱThere is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. Acceptable regimens include FOLFIRINOX or gemcitabine + albumin-bound paclitaxel. Subsequent chemoradiation is sometimes included. Most NCCN Member Institutions prefer neoadjuvant therapy at a high-volume center. Performing surgery with a high likelihood of a positive margin is not recommended.

^jSee Principles of Diagnosis, Imaging and Staging #8 (PANC-A).

^kSee Principles of Palliation and Supportive Care (PANC-E).

^lSee Principles of Diagnosis, Imaging and Staging #1 and #7 (PANC-A).

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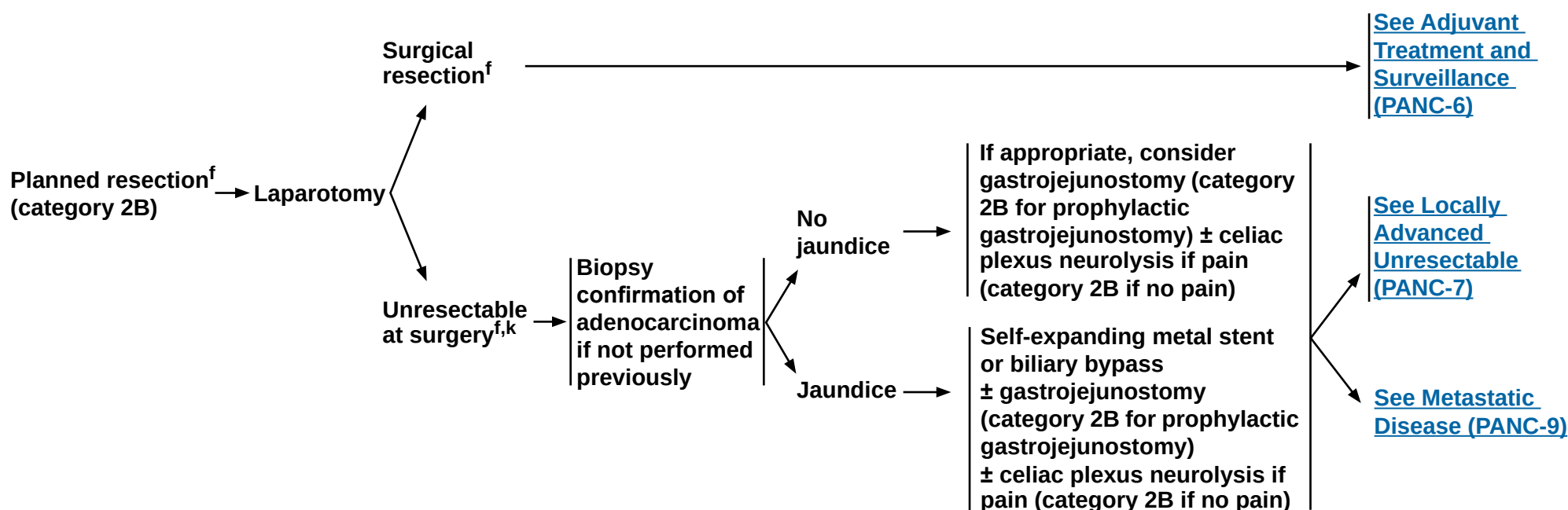
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Pancreatic Adenocarcinoma

BORDERLINE RESECTABLE^{d,e} NO METASTASES, PLANNED RESECTION

WORKUP

TREATMENT



^dSee Principles of Diagnosis, Imaging, and Staging (PANC-A).

^eSee Criteria Defining Resectability Status (PANC-B).

^fSee Principles of Surgical Technique (PANC-C) and Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting (PANC-D).

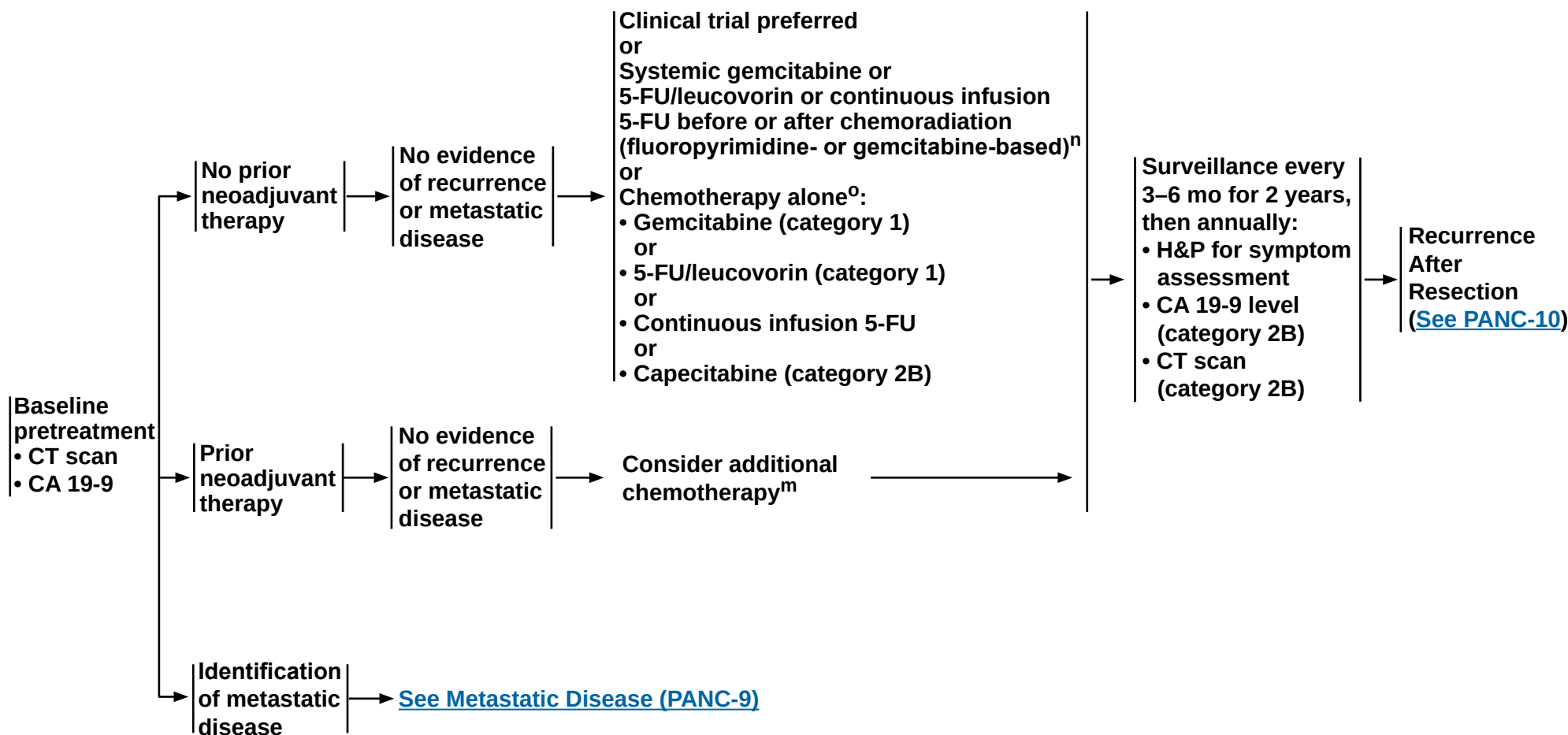
^kSee Principles of Palliation and Supportive Care (PANC-E).

Note: All recommendations are category 2A unless otherwise indicated.

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POSTOPERATIVE ADJUVANT TREATMENT^m

SURVEILLANCE



^mPatients who have received neoadjuvant chemoradiation or chemotherapy may be candidates for additional chemotherapy following surgery and multidisciplinary review. Adjuvant treatment should be administered to patients who have not had neoadjuvant chemotherapy and who have adequately recovered from surgery; treatment should be initiated within 12 weeks. If systemic chemotherapy precedes chemoradiation, restaging with imaging should be done after each treatment modality.

ⁿSee [Principles of Radiation Therapy \(PANC-F\)](#).

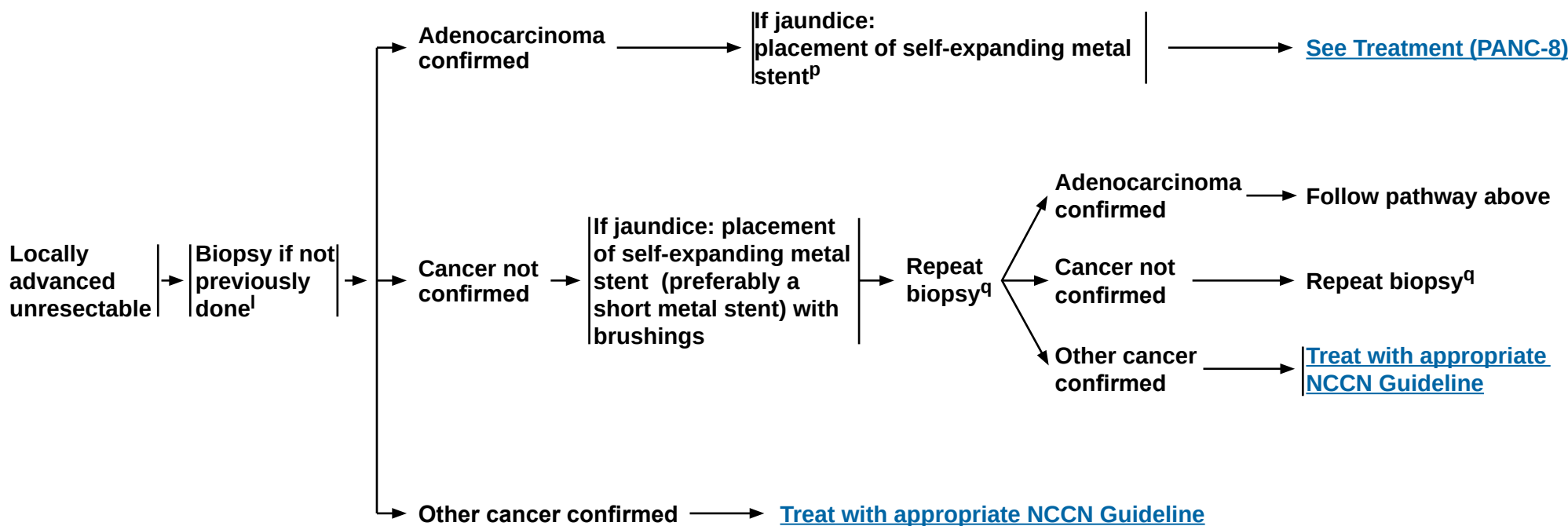
^oSee [Principles of Chemotherapy \(PANC-G\)](#).

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

LOCALLY ADVANCED UNRESECTABLE

WORKUP



^lSee Principles of Diagnosis, Imaging and Staging #1 and #7 (PANC-A).

^pUnless biliary bypass performed at time of laparoscopy or laparotomy.

^qEUS-FNA ± core biopsy at a center with multidisciplinary expertise is preferred.

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**LOCALLY
ADVANCED
UNRESECTABLE**

TREATMENT

SECOND-LINE THERAPY^W

Good
performance
status^r

Chemotherapy:

- Clinical trial preferred
or
- FOLFIRINOX^{o,x}
or
- Gemcitabine^o
or
- Gemcitabine + albumin-bound paclitaxel^{o,x} or other gemcitabine-based combination therapy^o
or
- Capecitabine^o or continuous infusion 5-FU^o (category 2B)
or
- Fluoropyrimidine + oxaliplatin^o (category 2B)

Chemoradiation in selected patients (locally advanced without systemic metastases), preferably following an adequate course of chemotherapy^{n,s,t,u}

Good
performance
status^{r,v}

- Clinical trial (preferred)
or
- Fluoropyrimidine-based chemotherapy if previously treated with gemcitabine-based therapy^o
or
- Gemcitabine-based therapy if previously treated with fluoropyrimidine-based therapy^o
or
- Chemoradiation if not previously given and if primary site is the sole site of progressionⁿ

Poor
performance
status

Palliative
and
best
supportive
care^k

Poor
performance
status

Gemcitabine^o (category 1)
or
Palliative and best supportive care^{k,n}

^kSee [Principles of Palliation and Supportive Care \(PANC-E\)](#).

ⁿSee [Principles of Radiation Therapy \(PANC-F\)](#).

^oSee [Principles of Chemotherapy \(PANC-G\)](#).

^rDefined as ECOG 0-1 with good pain management, patent biliary stent, and adequate nutritional intake.

^sLaparoscopy as indicated to evaluate distant disease.

^tChemoradiation should be reserved for patients who do not develop metastatic disease while receiving systemic chemotherapy.

^uBased on preliminary data from the LAP-07 trial, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy. Chemoradiation may improve local control and delay the need for resumption therapy. (Huguet F, Hammel P, Vernerey D, et al. Impact of chemoradiation on local control and time without treatment in patients with locally advanced pancreatic cancer included in the international phase III LAP 07 study. J Clin Oncol 2014; 32:5s. Abstract 4001.)

^vPatients with a significant response to therapy may be considered for surgical resection.

^wBest reserved for patients who maintain a good performance status.

^xThe recommendations for FOLFIRINOX and gemcitabine + albumin-bound paclitaxel in patients with locally advanced disease are based on extrapolations from randomized trials in patients with metastatic disease.

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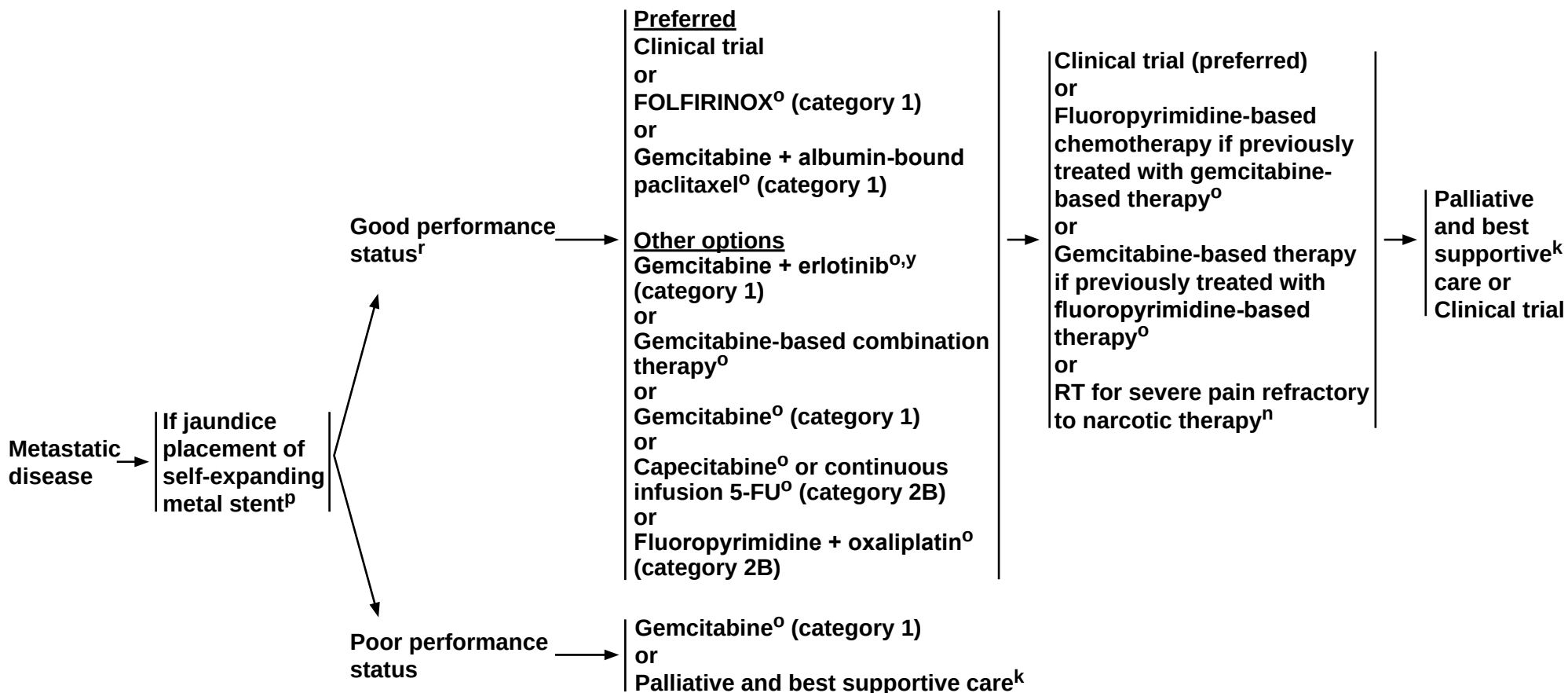
NCCN Guidelines Version 2.2015

Pancreatic Adenocarcinoma

METASTATIC DISEASE

TREATMENT

SECOND-LINE THERAPY^w



^kSee Principles of Palliation and Supportive Care (PANC-E).

ⁿSee Principles of Radiation Therapy (PANC-F).

^oSee Principles of Chemotherapy (PANC-G).

^pUnless biliary bypass performed at time of laparoscopy or laparotomy.

^rDefined as ECOG 0-1 with good pain management, patent biliary stent, and adequate nutritional intake.

^wBest reserved for patients who maintain a good performance status.

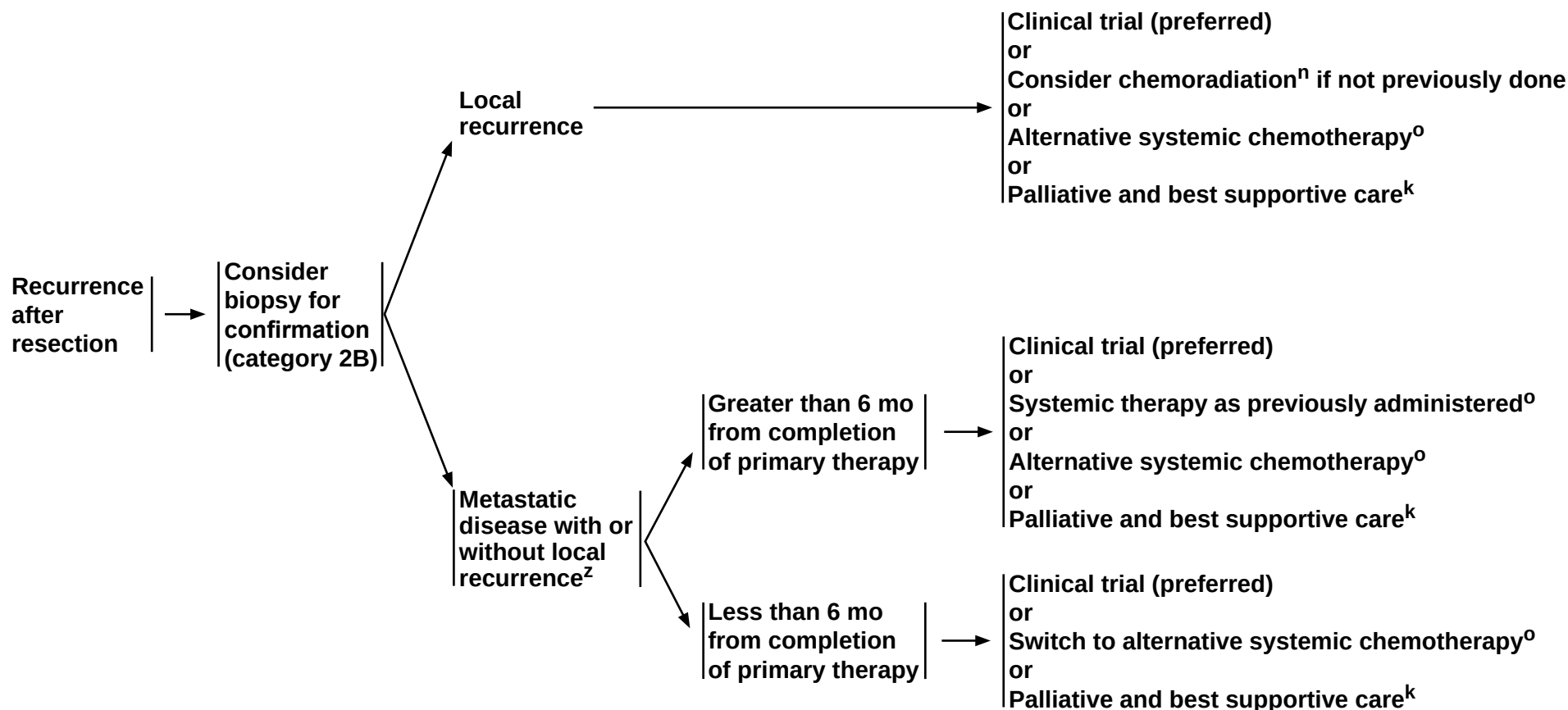
^yAlthough this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.

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RECURRENCE AFTER RESECTION

SECOND-LINE THERAPY^w



^kSee Principles of Palliation and Supportive Care (PANC-E).

ⁿSee Principles of Radiation Therapy (PANC-F).

^oSee Principles of Chemotherapy (PANC-G).

^wBest reserved for patients who maintain a good performance status.

^zFor more information about the treatment of isolated pulmonary metastases, [see Discussion](#).

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PRINCIPLES OF DIAGNOSIS, IMAGING, AND STAGING

- #1 Decisions about diagnostic management and resectability should involve multidisciplinary consultation at a high-volume center with reference to appropriate high-quality imaging studies to evaluate the extent of disease. Resections should be done at institutions that perform a large number (at least 15–20) of pancreatic resections annually.**
- #2 High-quality dedicated imaging of the pancreas should be performed at presentation (even if standard CT imaging is already available) and following neoadjuvant treatment to provide adequate staging and assessment of resectability status.**
- #3 Imaging should include dedicated pancreatic CT (preferred) or MRI.**
- Multi-detector computed tomography (MDCT) angiography, performed by acquiring thin, preferably sub-millimeter, axial sections using a dual-phase pancreatic protocol, with images obtained in the pancreatic and portal venous phase of contrast enhancement, is the preferred imaging tool for dedicated pancreatic imaging.¹ Scan coverage can be extended to cover the chest and pelvis for complete staging as per institutional preferences. Multiplanar reconstruction is preferred as it allows precise visualization of the relationship of the primary tumor to the mesenteric vasculature as well as detection of subcentimeter metastatic deposits. See MDCT Pancreas Protocol, PANC-A (3 of 4).
 - MRI is most commonly used as a problem-solving tool, particularly for characterization of CT-indeterminate liver lesions and when suspected pancreatic tumors are not visible on CT or when contrast-enhanced CT cannot be obtained (as in cases with severe allergy to iodinated intravenous contrast material). This preference for using MDCT as the main imaging tool in many hospitals and imaging centers, is mainly due to the higher cost and lack of widespread availability of MRI compared to CT. See MRI Pancreas Protocol, PANC-A (4 of 4).
 - MR cholangiopancreatography without IV contrast should not be utilized in the staging of pancreatic cancer, except in cases of renal failure or other contraindications to administration of gadolinium intravenous contrast.
- #4 The decision regarding resectability status should be made by consensus at multidisciplinary meetings/discussions following the acquisition of dedicated pancreatic imaging including complete staging. Use of a radiology staging reporting template is preferred to ensure complete assessment and reporting of all imaging criteria essential for optimal staging, which will improve the decision-making process.¹**

[Continued on next page](#)

¹Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the society of abdominal radiology and the American pancreatic association. Gastroenterology. 2014 Jan; 146 (1):291-304 and Radiology. 2014 Jan; 270 (1):248-60.

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PRINCIPLES OF DIAGNOSIS, IMAGING, AND STAGING

- #5** The role of PET/CT (without iodinated intravenous contrast) scan remains unclear. Diagnostic CT or MRI with IV contrast as discussed above in conjunction with functional PET imaging can be used per institutional preference. PET/CT scan may be considered after formal pancreatic CT protocol in high-risk* patients to detect extra pancreatic metastases. It is not a substitute for high-quality, contrast-enhanced CT.
- #6** EUS is not recommended as a routine staging tool. In select cases, EUS may be complementary to CT for staging.
- #7** EUS-FNA is preferable to a CT-guided FNA in patients with resectable disease because of better diagnostic yield, safety, and potentially lower risk of peritoneal seeding with EUS-FNA when compared with the percutaneous approach. Biopsy proof of malignancy is not required before surgical resection, and a non-diagnostic biopsy should not delay surgical resection when the clinical suspicion for pancreatic cancer is high.
- #8** Diagnostic staging laparoscopy to rule out metastases not detected on imaging (especially for body and tail lesions) is used in some institutions prior to surgery or chemoradiation, or selectively in patients who are at higher risk* for disseminated disease.
- #9** Positive cytology from washings obtained at laparoscopy or laparotomy is equivalent to M1 disease. If resection has been done for such a patient, he or she should be treated for M1 disease.

[Continued on next page](#)

*Indicators of high-risk patients may include borderline resectable disease, markedly elevated CA 19-9, large primary tumors, or large regional lymph nodes.

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PRINCIPLES OF DIAGNOSIS, IMAGING, AND STAGING

MDCT Pancreatic Adenocarcinoma Protocol¹

Parameters	Details
Scan Type	Helical (preferably 64-multidetector row scanner or more)
Section thickness	Thinnest possible (<3 mm). Preferably submillimeter (0.5–1 mm) if available
Interval	Same as section thickness (no gap)
Oral contrast agent	Neutral contrast (positive oral contrast may compromise the three dimensional [3D] and maximum intensity projection [MIP] reformatted images)
Intravenous contrast	Iodine-containing contrast agents (preferably high concentration [>300 mg I/L]) at an injection rate of 3–5 mL/sec. Lower concentration contrast can be used if low Kv setting is applied
Scan acquisition timing	Pancreatic parenchymal phase at 40–50 and portal venous phase at 65–70 sec, following the commencement of contrast injection
Image reconstruction and display	<ul style="list-style-type: none"> - Axial images and multiplanar reformats (in the coronal, and per institutional preference, sagittal plane) at 2–3 mm interval reconstruction - MIP or 3D volumetric thick section for vascular evaluation (arteries and veins)

[Continued on next page](#)

¹Adapted from: Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the society of abdominal radiology and the American pancreatic association. Gastroenterology. 2014 Jan; 146 (1):291-304.

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PRINCIPLES OF DIAGNOSIS, IMAGING, AND STAGING

MRI Pancreatic Adenocarcinoma Protocol²

Sequences	Plane	Slice thickness
T2-weighted single-shot fast spin-echo (SSFSE)	Coronal +/- axial	<6 mm
T1-weighted in-phase and opposed-phase gradient echo (GRE)	Axial	<6 mm
T2-weighted fat-suppressed fast spin-echo (FSE)	Axial	<6 mm
Diffusion-weighted imaging (DWI)	Axial	<6 mm
Pre and dynamic post IV contrast administration (gadolinium ³) Three-dimensional [3D] T1-weighted fat-suppressed gradient-echo (in pancreatic, portal venous, and equilibrium phases)	Axial	Thinnest possible 2–3 mm (4–6 mm if overlapping)
T2-weighted MRCP (preferably three-dimensional [3D], fast relaxation fast spin-echo sequence [FRFSE])	Coronal	<3 mm

²Sheridan MB1, Ward J, Guthrie JA, et al. Dynamic contrast-enhanced MR imaging and dual-phase helical CT in the preoperative assessment of suspected pancreatic cancer: a comparative study with receiver operating characteristic analysis. AJR Am J Roentgenol. 1999 Sep; 173 (3):583-90.

³Unenhanced MRI can be obtained in cases of renal failure or contraindication to gadolinium intravenous contrast if enhanced CT cannot be obtained due to severe iodinated contrast allergy.

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CRITERIA DEFINING RESECTABILITY STATUS¹

Resectability Status	Arterial	Venous
Resectable	No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or $\leq 180^\circ$ contact without vein contour irregularity
Borderline Resectable ²	<p><u>Pancreatic head /uncinate process:</u></p> <ul style="list-style-type: none"> • Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of $\leq 180^\circ$ • Presence of variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present as it may affect surgical planning. <p><u>Pancreatic body/tail:</u></p> <ul style="list-style-type: none"> • Solid tumor contact with the CA of $\leq 180^\circ$ • Solid tumor contact with the CA of $>180^\circ$ without involvement of the aorta and with intact and uninvolved gastroduodenal artery [some members prefer this criteria to be in the unresectable category]. 	<ul style="list-style-type: none"> • Solid tumor contact with the SMV or PV of $>180^\circ$, contact of $\leq 180^\circ$ with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC)
Unresectable ²	<ul style="list-style-type: none"> • Distant metastasis (including non-regional lymph node metastasis) <p><u>Head/uncinate process:</u></p> <ul style="list-style-type: none"> • Solid tumor contact with SMA $>180^\circ$ • Solid tumor contact with the CA $>180^\circ$ • Solid tumor contact with the first jejunal SMA branch <p><u>Body and tail</u></p> <ul style="list-style-type: none"> • Solid tumor contact of $>180^\circ$ with the SMA or CA • Solid tumor contact with the CA and aortic involvement 	<p><u>Head/uncinate process</u></p> <ul style="list-style-type: none"> • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) • Contact with most proximal draining jejunal branch into SMV <p><u>Body and tail</u></p> <ul style="list-style-type: none"> • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

¹Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the society of abdominal radiology and the American pancreatic association. Gastroenterology. 2014 Jan; 146 (1):291-304.

²Solid tumor contact may be replaced with increased hazy density/stranding of the fat surrounding the peri-pancreatic vessels (typically seen following neoadjuvant therapy); this finding should be reported on the staging and follow up scans. Decision on resectability status should be made in these patients, in consensus at multidisciplinary meetings/discussions

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PRINCIPLES OF SURGICAL TECHNIQUE

Pancreatoduodenectomy (Whipple technique)

The goals of surgical extirpation of pancreatic carcinoma focus on the achievement of an R0 resection, as a margin-positive specimen is associated with poor long-term survival.^{1,2} Achievement of a margin-negative dissection must focus on meticulous perivascular dissection of the lesion in resectional procedures, recognition of the need for vascular resection and/or reconstruction, and the potential need for extra-pancreatic organ resection. Of course the biology of the cancer might not allow for an R0 resection even with the most meticulous surgery.

- Medial dissection of pancreatic head lesions is best achieved by complete mobilization of the portal and SMVs from the uncinate process (assuming no evidence of tumor infiltration). Skeletalization of the lateral, posterior, and anterior borders of the superior mesenteric artery down to the level of the adventitia will maximize uncinate yield and radial margin.^{3,4}
- In the absence of frank venous occlusion noted on preoperative imaging, the need for lateral venorrhaphy or complete portal or SMV resection and reconstruction to achieve an R0 resection may be suggested but is often not known until division of the pancreatic neck has occurred. Tethering of the carcinoma to the lateral wall of the PV is not uncommon and requires careful dissection to free the vein from the pancreatic head if in fact it is possible to do so. Differentiation of tumor infiltration into the vein wall from tumor-related desmoplasia is frequently impossible to ascertain. Data support an aggressive approach to partial or complete vein excision if tumor infiltration is suspected, although acceptance of this concept (particularly with respect to vein resection) is not universal.
- While further data with respect to arterial resection are clearly needed, judicious utilization of this technique would appear to be reasonable in very select populations.

Distal Pancreatectomy

The goals of left-sided resection are similar to those of pancreatoduodenectomy, although they are often more difficult to achieve due to the advanced stage at which most of these cancers are discovered.

- An R0 distal pancreatectomy for adenocarcinoma mandates en bloc organ removal beyond that of the spleen alone in up to 40% of patients.^{5,6}
- Similar to the Whipple procedure, lateral venorrhaphy, vein excision and reconstruction, and dissection to the level of the celiac axis and SMA adventitia should be performed if complete tumor clearance can be achieved.^{5,7}
- Utilization of radical resections is associated with an increase in blood loss, transfusion requirements, operating time, length of stay, and whether morbidity/mortality remains acceptable.^{5,7}
- Spleen preservation is not indicated in adenocarcinoma.

¹Bilimoria KY, Talamonti MS, Sener SF, et al. Effect of hospital volume on margin status after pancreaticoduodenectomy for cancer. J Am Coll Surg. Oct 2008;207(4):510-519.

²Winter JM, Cameron JL, Campbell KA, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. J Gastrointest Surg. Nov 2006;10(9):1199-1210; discussion 1210-1191.

³Yeo TP, Hruban RH, Leach SD, et al. Pancreatic cancer. Curr. Probl. Cancer. Jul-Aug 2002;26(4):176-275.

⁴Nakeeb A, Lillemoe KD, Grosfeld JL. Surgical techniques for pancreatic cancer. Minerva Chir. Apr 2004;59(2):151-163.

⁵Shoup M, Conlon KC, Klimstra D, et al. Is extended resection for adenocarcinoma of the body or tail of the pancreas justified? J Gastro Surg. Dec 2003;7(8):946-952; discussion 952.

⁶Christein JD, Kendrick ML, Iqbal CW, Nagorney DM, Farnell MB. Distal pancreatectomy for resectable adenocarcinoma of the body and tail of the pancreas. J Gastrointest Surg. Sep-Oct 2005;9(7):922-927.

⁷Strasberg SM, Linehan DC, Hawkins WG. Radical antegrade modular pancreatosplenectomy procedure for adenocarcinoma of the body and tail of the pancreas: ability to obtain negative tangential margins. J Am Coll Surg. Feb 2007;204(2):244-249.

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PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING

The primary purpose of pathologic analysis of the pancreatic specimen is to determine the pathologic stage of the tumor by evaluating the type, grade, size, and extent of the cancer.

Whipple Specimen

• Specimen orientation

- ▶ Specimen orientation and inking involves both the pathologist and surgeon as this will help to ensure accurate assessment of the size and extent of the tumor. There should be either direct communication between the surgeon and pathologist for proper orientation and margin identification, or the surgeon should identify the important margins with a clearly understood and documented method (eg, written on the pathology requisition); for example: stitch on posterior margin, safety pin on the retroperitoneal/uncinate margin.

• Margins

- ▶ Definitions of the margins and uniformity of nomenclature are critical to accurate reporting

- ◊ **SMA (retroperitoneal/uncinate) Margin:** The most important margin is the soft tissue directly adjacent to the proximal 3–4 cm of the superior mesenteric artery. This margin is often referred to as the “retroperitoneal margin” or “posterior margin,” but has also been referred to as the “uncinate margin” or “mesenteric margin.” More recently, this margin has been referred to as the “SMA margin” to correlate with its location on the specimen. Radial rather than en face sections of this margin will more clearly demonstrate how closely this margin is approached by tumor. The simple step of palpating the specimen can help guide the pathologist as to the best spot along the SMA margin to select for sampling.
- ◊ **Posterior Margin:** This margin is from the posterior caudad aspect of the pancreatic head that merges with the uncinate margin and that appears to be covered by loose connective tissue. Radial rather than en face sections of this margin will more clearly demonstrate whether it is involved by tumor. In some instances this margin can be included in the same section as the SMA margin section.
- ◊ **Portal Vein Groove Margin:** This is the smooth-surfaced groove on the posterior-medial surface of the pancreatic head that rests over the PV. Radial rather than en face sections of this margin will more clearly demonstrate whether it is involved by tumor and also will provide the distance of the tumor from the margin. As is true for the posterior margin, in some instances this margin can be included in the same section as the SMA margin section.
- ◊ **Portal Vein Margins:** If an en bloc partial or complete vein resection is added to the surgical specimen it should be marked separately. En face proximal and distal end margins of the vein should be separately submitted as Proximal Portal Vein Margin and Distal Portal Vein Margin. A section documenting tumor invasion into the vein wall should also be submitted. If feasible, this section should be a full thickness of the vein wall demonstrating the depth of tumor invasion as this has been shown to have prognostic value.¹
- ◊ **Pancreatic Neck (transection) Margin:** This is the en face section of the transected pancreatic neck. The section should be placed into the cassette with the true margin facing up so that the initial section into the block represents the true surgical margin.
- ◊ **Bile Duct Margin:** This is the en face section of the bile duct end. The section should be removed from the unopened duct and placed into the cassette with the true margin facing up so that the initial section into the block represents the true surgical margin.
- ▶ Other margins analyzed in Whipple specimens include the proximal and distal enteric margins (en face sections) and anterior surface (closest representative). The anterior surface is not a true margin, but identification and reporting of this surface when positive may portend a risk of local recurrence, and therefore should be reported in all cases.²⁻⁵
- ▶ Collectively, these pancreatic tissue surfaces constitute the circumferential transection margin. Designating the various specific margins with different colored inks will allow recognition on microscopy.

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PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING

- **Histologic sectioning**

- ▶ The approach to histologic sectioning is determined by the unique characteristics of the tumor, but is also influenced by institutional preferences, expertise, and experience. Options include axial, bi- or multi-valve slicing, and perpendicular sliding. Some experts in the field bisect the pancreas along probes placed in the bile and pancreatic ducts and then serially section along each half of the pancreas.
- ▶ Axial slicing provides an overall assessment of the epicenter of the tumor relative to the ampulla, bile duct, duodenum, and pancreas, and all of the pancreatic circumferential tissue margins mentioned above.
- ▶ There is no one correct way to dissect a Whipple specimen. The most important aspects of dissection are clear and accurate assessment of the margins.
- ▶ It is currently unknown what constitutes an adequate margin in pancreatic carcinoma resection specimens. A standardized definition of this would allow better stratification of patients into adjuvant regimens following surgical extirpation. For instance, if less than 1 mm clearance is associated with an unacceptably high incidence of local recurrence, then strong consideration for postoperative radiation therapy (RT) might be indicated if not received preoperatively. Tumor clearance should be reported in millimeters for all margins described above to allow prospective accumulation of these important data for future analysis.
- ▶ Attached organs resected with the specimen en bloc require serial sectioning to assess not only direct extension, but metastatic deposits as well. One section that demonstrates direct invasion of the organ and/or a separate metastatic deposit is required.
- ▶ Frozen section analysis of the pancreatic neck and bile duct is recommended. To avoid cautery artifact that may confound the frozen section, assess the pancreatic neck and bile duct at time of surgery by frozen section approximately 5 mm from the transection margin. If tumor is located within 5 mm of margins, consider further excision of the pancreas to ensure at least 5 mm of clearance.

Distal Pancreatectomy

- In left-sided resections the peripancreatic soft tissue margins and the pancreatic neck are assessed. Additionally, involvement of the splenic vessels should be documented and invasion of the spleen is important to determine, as direct tumor invasion constitutes a pT3 pathologic stage.
- Margins definitions are as follows:
 - ▶ Proximal Pancreatic (transection) Margin: A full en face section of the pancreatic body along the plane of transection. The section should be placed into the cassette with the true margin facing up so that the initial section into the block represents the true surgical margin. More than one block may be needed.
 - ▶ Anterior (cephalad) Peripancreatic (peripheral) Surface: This surface demonstrates the relationship between the tumor and the anterior or cephalad peripancreatic soft tissue and can be representative if grossly positive. Several such sections should be taken closest to the tumor to document absence of involvement; the exact number is dependent on the degree of ambiguity of gross involvement.
 - ▶ Posterior (caudad) Peripancreatic (peripheral) Margin: This margin demonstrates the relationship between the tumor and the posterior or caudad peripancreatic soft tissue and can be representative if grossly positive. Several such sections should be taken closest to the tumor to document absence of involvement; the exact number is dependent on the degree of ambiguity of gross involvement.

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PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING

Reporting

The NCCN Pancreatic Cancer Panel currently supports pathology synoptic reports from the College of American Pathologists (CAP). The proposal included herein is an abbreviated minimum analysis of pancreatic cancer specimens from the CAP recommendations. In addition to the standard TNM staging, other variables are included all of which have prognostic implications in the evolution of this disease.^{6,7}

Specimen type

- Tumor size (obtained from careful gross measurement of the largest dimension of the tumor in cm.)
 - Histologic grade (G (x-4))
 - Primary tumor extent of invasion (T (x-4))
 - Regional lymph nodes (N (x-1))^a
 - ▶ # Nodes recovered
 - ▶ # Nodes involved
 - Metastases (M (0-1))
 - Margins: (Involvement should be defined and surgical clearance measured in mm)
 - ▶ Whipple resection:
 - ◊ SMA (retroperitoneal/uncinate) Margin
 - ◊ Posterior Margin
 - ◊ Portal Vein Groove Margin
 - ◊ Pancreatic Neck (transection) Margin
 - ◊ Bile Duct Margin
 - ◊ Enteric Margins
 - ◊ Anterior Surface
 - ▶ Distal pancreatectomy:
 - ◊ Proximal Pancreatic (transection) Margin
 - ◊ Anterior (cephalad) Peripancreatic (peripheral) Surface (optional)
 - ◊ Posterior (caudad) Peripancreatic (peripheral) Margin
 - Lymphatic (small vessel) Invasion (L)
 - Vascular (large vessel) Invasion (V)
 - Perineural Invasion (P)
 - Additional pathologic findings
 - ▶ Pancreatic Intraepithelial Neoplasia
 - ▶ Chronic Pancreatitis
- Final stage: G, T, N, M, L, V, P

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^aEvery effort should be made to identify all regional lymph nodes within the pancreatectomy specimen ([see Discussion](#)).

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PATHOLOGIC ANALYSIS: SPECIMEN ORIENTATION, HISTOLOGIC SECTIONS, AND REPORTING

References

- ¹Fukuda S, Oussoultzoglou E, Bachellier P, et al. Significance of the depth of portal vein wall invasion after curative resection for pancreatic adenocarcinoma. Arch surg Feb 2007;142(2):172-179; discussion 180.
- ²Verbeke CS. Resection margins and R1 rates in pancreatic cancer--are we there yet? Histopathol Jun 2008;52(7):787-796.
- ³The Royal College of Pathologists. Standards and minimum datasets for reporting cancers. Minimum dataset for the histopathological reporting of pancreatic, ampulla of Vater and bile duct carcinoma. The Royal College of Pathologists. 2002.
- ⁴Classification of pancreatic cancer. Japan Pancreas Society. 2nd ed. Tokyo: Kanehara; 2003.
- ⁵Hruban RH, Pitman MB, Klimstra DS. Tumors of the Pancreas. Atlas of Tumor Pathology, 4th series, fascicle 6. Washington, D.C.: American Registry of Pathology; Armed Forces Institutes of Pathology; 2007.
- ⁶Mitsunaga S, Hasebe T, Iwasaki M, Kinoshita T, Ochiai A, Shimizu N. Important prognostic histological parameters for patients with invasive ductal carcinoma of the pancreas. Cancer Sci Dec 2005;96(12):858-865.
- ⁷Gebhardt C, Meyer W, Reichel M, Wunsch PH. Prognostic factors in the operative treatment of ductal pancreatic carcinoma. Langenbecks Arch Surg Jan 2000;385(1):14-20.

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PRINCIPLES OF PALLIATION AND SUPPORTIVE CARE^a

Objectives: Prevent and ameliorate suffering while ensuring optimal quality of life

- **Biliary obstruction**
 - ▶ Endoscopic biliary metal stent (preferred method)
 - ▶ Percutaneous biliary drainage with subsequent internalization
 - ▶ Open biliary-enteric bypass
- **Gastric outlet obstruction**
 - ▶ Good performance status
 - ◊ Gastrojejunostomy (open or laparoscopic) ± J-tube
 - ◊ Consider enteral stent^b
 - ▶ Poor performance status
 - ◊ Enteral stent^b
 - ◊ Venting percutaneous endoscopic gastrostomy (PEG) tube for gastric decompression
- **Severe tumor-associated abdominal pain**
 - ▶ EUS-guided celiac plexus neurolysis (fluoroscopic- or CT-guided if unavailable)
 - ▶ Consider palliative radiation with or without chemotherapy if not already given as part of primary therapy regimen
- **Depression, pain, and malnutrition**
 - ▶ Formal Palliative Medicine Service evaluation when appropriate ([See NCCN Guidelines for Supportive Care](#))
 - ▶ Nutritional evaluation when appropriate.
- **Pancreatic exocrine insufficiency**
 - ▶ Pancreatic enzyme replacement
- **Thrombembolic disease**
 - ▶ Low-molecular-weight heparin preferred over warfarin

^aPalliative surgical procedures are best reserved for patients with a longer life expectancy.

^bPlacement of an enteral stent is particularly important for patients with poor performance status and should be done after biliary drainage is assured.

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PRINCIPLES OF RADIATION THERAPY

General Principles:

- Patients with pancreatic cancer are best managed by a multidisciplinary team.¹
- Recommendations for RT for such patients are typically made based upon five clinical scenarios: 1) neoadjuvant/resectable; 2) borderline resectable; 3) locally advanced/unresectable; 4) adjuvant/resectable; and 5) palliative. For definitions of these scenarios, [See Criteria Defining Resectability Status \(PANC-B\)](#).
- Staging is optimally determined with modern contrast-enhanced abdominal CT (3-D CT) and/or MRI imaging with thin cuts through the pancreas along with an EUS.
- If patients present with biliary obstruction (jaundice/elevated direct bilirubin), plastic or metal stents should be placed prior to initiation of RT. A percutaneous drain can also be used if ERCP stent placement is unsuccessful.
- The role of laparoscopic evaluation prior to chemoradiation is controversial, although standard at some institutions.
- Ideally, patients should be treated on clinical trials when available. Radiation is typically given concurrently with chemotherapy, except in the palliative setting.

Standard Recommendations:

****Note:** It is not known whether one regimen is necessarily more effective than another; hence, these are given as examples of commonly utilized regimens; however, others based on similar principles are acceptable.

Neoadjuvant Resectable/Borderline Resectable:

- No standard treatment regimen currently exists for neoadjuvant resectable or borderline resectable pancreatic cancer. Neoadjuvant therapy for patients with resectable tumors should ideally be conducted in a clinical trial. Generally, use similar paradigms as for locally advanced unresectable disease.
 - ▶ Upfront fluoropyrimidine (CI-5-FU or capecitabine-based) chemoradiation.^{2,3}
 - ▶ Upfront gemcitabine-based chemoradiation.⁴
 - ▶ Induction chemotherapy (2–6 cycles) followed by 5-FU- or gemcitabine-based chemoradiation.⁵
- Ideally, surgical resection should be attempted 4–8 weeks following chemoradiation. Surgery can be performed >8 weeks following chemoradiation; however, radiation-induced fibrosis may potentially make surgery more difficult.

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PRINCIPLES OF RADIATION THERAPY

Unresectable/Locally Advanced (non-metastatic):

- ▶ Induction chemotherapy followed by 5-FU or gemcitabine-based chemoradiation^{a,7,8}
- ▶ Upfront fluoropyrimidine (CI 5-FU or capecitabine)-based chemoradiation in select patients.
- ▶ Upfront gemcitabine-based chemoradiation in select patients.^{9,10}
- Options include:
 - ▶ RT 45–54 Gy in 1.8–2.5 Gy fractions (doses higher than 54 Gy may be considered if clinically appropriate) or
 - ▶ 36 Gy in 2.4 Gy fractions.¹¹
- Following chemoradiation, additional maintenance chemotherapy is sometimes used, especially if tumors are still unresectable.
- In cases where 1) it is highly unlikely that patients will become resectable (complete encasement of superior mesenteric/celiac arteries); 2) there are suspicious metastases; and 3) patients may not be able to tolerate chemoradiation, then it may be reasonable to start with chemotherapy (2–6 cycles) followed by definitive chemoradiation if there is no evidence of metastatic progression.
- If patients present with poorly controlled pain or local obstructive symptoms, it may be preferable to start with upfront chemoradiation.
- No standard total dose or dose per fraction has been established for SBRT; therefore, it should preferably be utilized as part of a clinical trial.¹²

Adjuvant:

- Treatment options following pancreaticoduodenectomy or distal pancreatectomy include:
 - ▶ Upfront fluoropyrimidine- (CI 5-FU or capecitabine) or gemcitabine-based chemoradiation followed by maintenance 5-FU or gemcitabine.¹³
 - ▶ Gemcitabine or CI 5-FU (1 cycle) followed by CI 5-FU/RT followed by maintenance gemcitabine or CI 5-FU.¹⁴
 - ▶ Gemcitabine or bolus 5-FU/leucovorin or continuous infusion 5-FU¹⁵
 - ▶ Gemcitabine or bolus 5-FU/leucovorin for 2–6 cycles followed by fluoropyrimidine- (CI 5-FU or capecitabine) based chemoradiation.¹⁶
- RT 45–46 Gy in 1.8–2 Gy fractions to the tumor bed, surgical anastomoses (hepaticojejunostomy and gastrojejunostomy may be omitted if clinically appropriate), and adjacent lymph nodes, followed by an additional 5–9 Gy to the tumor bed and anastomoses, if clinically appropriate.¹⁷

Palliative:

- [See Principles of Palliation and Supportive Care \(PANC-E\).](#)
 - ▶ RT alone to the primary tumor plus a margin (Typically 25–36 Gy in 2.4–5 Gy fractions) is reasonable for patients with metastatic disease who require local palliation for obstruction, pain, or bleeding.¹⁸
 - ▶ Palliative RT can also be considered for patients who are elderly and/or not candidates for definitive therapy because of comorbidities.
 - ▶ Metastatic sites causing pain may also be palliated with RT.

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^aBased on preliminary data from the LAP-07 trial, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy. Chemoradiation may improve local control and delay the need for resumption therapy. (Huguet F, Hammel P, Vernerey D, et al. Impact of chemoradiation on local control and time without treatment in patients with locally advanced pancreatic cancer included in the international phase III LAP 07 study. J Clin Oncol 2014; 32:5s. Abstract 4001.)

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PRINCIPLES OF RADIATION THERAPY

Radiation Therapy Treatment Planning Principles:

- Patients should undergo a CT simulation (thin slices through the pancreas/bed and locoregional nodal basins) with IV (assuming adequate kidney function) and oral contrast. For resected cases, preoperative CT scans and strategically placed surgical clips are used to determine the tumor bed, ideally with the surgeon's assistance. In the neoadjuvant, borderline, and locally advanced settings the pancreatic gross tumor volume (GTV) and pathologic nodes (minimum >1 cm) are contoured with assistance from structural (CT/MRI) and functional imaging (PET).^{19,20}
- The planning target volume (PTV) should be defined per the ICRU-62 guidelines.²¹ A GTV should be defined for intact pancreatic tumors. For adjuvant cases, a clinical target volume (CTV) includes high-risk peri-pancreatic lymph nodes, anastomoses (hepaticojejunostomy and gastrojejunostomy may be omitted if clinically appropriate), pancreatic tumor bed derived from presurgical imaging, and strategically placed surgical clips. CTV expansions are needed to include possible microscopic disease. Further expansion to PTV includes internal target volume (ITV) for target/breathing motion and additional patient set-up error margin (SM).²²⁻²⁴ Image guidance methods should be considered when constructing the PTV. Organs at risk (OARs) should also be contoured and evaluated in the DVH.
- Elective nodal irradiation (ENI) is commonly used for adjuvant cases but is controversial for unresectable/neoadjuvant/borderline resectable cases.¹¹ Standard margin expansions for unresectable cases include the gross tumor and any pathologic lymph nodes (GTV) plus a 0.5–1.5 cm margin to target microscopic extension (CTV) and an additional 0.5–2 cm volume to account for tumor/breathing motion and patient set-up errors (PTV). With these expansions, peripancreatic nodes are generally included. 3-D conformal RT (3D-CRT) or intensity-modulated RT (IMRT) with breathhold/gating techniques can result in improved PTV coverage with decreased dose to OARs.^{25,26} With SBRT, smaller margins are used (0.2–0.5 cm) and the PTV does not cover locoregional elective nodal regions.²⁷ If small GTV margin expansions are used for CTV and PTV, breathing motion and set-up error should be evaluated or controlled per the AAPM Task Group 76 guidelines.²⁸
- IORT is delivered with electron beam RT (IOERT) or high-dose-rate brachytherapy (HDR-IORT). IORT is generally delivered in a single fraction and in combination with adjuvant or neoadjuvant chemoradiation. The role of IORT is controversial and should only be performed at specialized centers. It is sometimes used in cases where surgical resection may result in close or involved margins.²⁹
- It is imperative to evaluate the dose-volume histogram (DVH) of the PTV and critical normal structures such as the liver, kidneys, spinal cord, liver, and bowel.
- ([See Table 1. Normal Tissue Dose Volume Recommendations \[PANC-F, 4 of 6\]](#)) While these examples of limits are empirical they differ based on dose per fraction, total dose delivered, and disease status (adjuvant vs. unresectable). Studies have shown that the tolerability of radiation is largely dependent on PTV size/ENI, types of concurrent systemic/targeted therapy, and whether conformal (3-D, IMRT, SBRT) vs. conventional radiation is used.

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PRINCIPLES OF RADIATION THERAPY

- Fractionated RT is typically delivered as 30–55 Gy over ~3–6 weeks (1.8–3.0 Gy/fraction, using lower dose per fraction at higher cumulative doses while respecting normal tissue constraints) with concurrent 5-FU/capecitabine or gemcitabine as a radiosensitizer. Doses above 55 Gy may be possible in select cases; however, data are limited and normal tissue dose limits (see Table 1) should be maintained. For resected cases, 45 Gy is delivered to the tumor bed, surgical anastomosis (hepaticojejunostomy and gastrojejunostomy may be omitted if clinically appropriate), and regional lymph nodes. Additional radiation (~5–15 Gy) may be administered to the tumor bed/area of involved margins and anastomoses paying careful attention to dose to bowel and stomach. The use of high-energy photon beams is preferred. SBRT is often delivered in 1–5 fractions ranging from 5–25 Gy per fraction. IORT can be delivered in a single fraction alone (15–20 Gy) or in combination with external beam RT (EBRT) (10–20 Gy).
- Several clinical trials (RTOG) now refer to atlases to assist with contouring and adjuvant RT planning (<http://www.rtog.org/CoreLab/ContouringAtlases.aspx>).

Table 1: Normal Tissue Dose Volume Recommendations

Structure	Unresectable/Preoperative Recommendations ^b	Adjuvant/Resected Recommendations ^c
Kidney (right and left)	Not more than 30% of the total volume can receive ≥18 Gy. If only one kidney is functional, not more than 10% of the volume can receive ≥18 Gy.	If two functioning kidneys present, not more than 50% of the right and 65% of the left kidney should receive >18 Gy. For IMRT planning mean dose to bilateral kidneys should be ≤18 Gy. If only one kidney is present not more than 15% should receive ≥18 Gy and no more than 30% should receive ≥14 Gy.
Stomach, duodenum, jejunum	Max dose ≤55 Gy; not more than 30% of the volume can be between 45 and 55 Gy.	Max dose ≤55 Gy; <10% of each organ volume can receive between 50–53.99 Gy. <15% of each organ volume can receive 45–49.99 Gy.
Liver	Mean dose cannot exceed 30 Gy.	Mean liver dose ≤25 Gy.
Spinal cord	Max dose to a volume of at least 0.03 cc must be ≤45 Gy.	Max dose ≤45 Gy.

^bAdapted from RTOG 0936 (3-D conformal, 1.8-50.5) and RTOG 1102 (IMRT, 2.2 to 55 Gy)

^cAdapted from RTOG 0848 (3-D or IMRT)

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PRINCIPLES OF RADIATION THERAPY

Table 2: Commonly Used Radiation Therapy Abbreviations

3D-CRT	3-D Conformal Radiation Therapy
IMRT	Intensity-Modulated Radiation Therapy
SBRT	Stereotactic Body Radiation Therapy
SABR	Stereotactic Ablative Radiation Therapy
EBRT	External Beam Radiation Therapy
ENI	Elective Nodal Irradiation
IORT	Intraoperative Radiation Therapy
DVH	Dose-Volume Histogram
GTV	Gross Tumor Volume
CTV	Clinical Target Volume
IM	Internal Margin: Variations in shape/size of CTV due to respiration and adjacent structures
ITV	Internal Target Volume: encompasses the CTV and IM (ITV = CTV + IM)
PTV	Planning Target Volume
BED	Biologically Effective Dose
OAR	Organ At Risk
ABC	Airway Breathing Control
IGRT	Image-Guided Radiation Therapy
4DCT	Four-Dimensional Computed Tomography
CBCT	Cone Beam Computed Tomography

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PRINCIPLES OF RADIATION THERAPY

References

- ¹Pawlik TM, Laheru D, Hruban RH, Coleman J, Wolfgang CL, Campbell K, Ali S, Fishman EK, Schulick RD, Herman JM, Johns Hopkins Multidisciplinary Pancreas Clinic Team. Evaluating the impact of a single-day multidisciplinary clinic on the management of pancreatic cancer. *Ann Surg Oncol* 2008 Aug; 15(8): 2081-2088.
- ²White RR, Hurwitz HI, Morse MA, Lee C, Anscher MS, Paulson EK, Gottfried MR, Baillie J, Branch MS, Jowell PS, McGrath KM, Clary BM, Pappas TN, Tyler DS. Neoadjuvant chemoradiation for localized adenocarcinoma of the pancreas. *Ann Surg Oncol* 2001 Dec; 8(10): 758-765.
- ³Le Scodan R, Mornex F, Girard N, Mercier C, Valette PJ, Ychou M, Bibeau F, Roy P, Scoazec JY, Partensky C. Preoperative chemoradiation in potentially resectable pancreatic adenocarcinoma: Feasibility, treatment effect evaluation and prognostic factors, analysis of the SFRO-FFCD 9704 trial and literature review. *Ann Oncol* 2009 Aug; 20(8): 1387-1396.
- ⁴Evans DB, Varadhachary GR, Crane CH, Sun CC, Lee JE, Pisters PW, Vauthey JN, Wang H, Cleary KR, Staerckel GA, Charnsangavej C, Lano EA, Ho L, Lenzi R, Abbruzzese JL, Wolff RA. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 2008 Jul 20; 26(21): 3496-3502.
- ⁵Varadhachary GR, Wolff RA, Crane CH, Sun CC, Lee JE, Pisters PW, Vauthey JN, Abdalla E, Wang H, Staerckel GA, Lee JH, Ross WA, Tamm EP, Bhosale PR, Krishnan S, Das P, Ho L, Xiong H, Abbruzzese JL, Evans DB. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 2008 Jul 20; 26(21): 3487-3495.
- ⁶Talamonti MS, Small W, Jr, Mulcahy MF, Wayne JD, Attaluri V, Colletti LM, Zalupski MM, Hoffman JP, Freedman GM, Kinsella TJ, Philip PA, McGinn CJ. A multi-institutional phase II trial of preoperative full-dose gemcitabine and concurrent radiation for patients with potentially resectable pancreatic carcinoma. *Ann Surg Oncol* 2006 Feb; 13(2): 150-158.
- ⁷Krishnan S, Rana V, Janjan NA, Varadhachary GR, Abbruzzese JL, Das P, Delclos ME, Gould MS, Evans DB, Wolff RA, Crane CH. Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. *Cancer* 2007 Jul 1; 110(1): 47-55.
- ⁸Huguet F, Girard N, Guerche CS, Hennequin C, Mornex F, Azria D. Chemoradiotherapy in the management of locally advanced pancreatic carcinoma: A qualitative systematic review. *J Clin Oncol* 2009 May 1; 27(13): 2269-2277.
- ⁹Blackstock AW, Tepper JE, Niedzwiecki D, Hollis DR, Mayer RJ, Tempero MA. Cancer and leukemia group B (CALGB) 89805: Phase II chemoradiation trial using gemcitabine in patients with locoregional adenocarcinoma of the pancreas. *Int J Gastrointest Cancer* 2003; 34(2-3): 107-116.
- ¹⁰Loehrer PJ Sr, Feng Y, Cardenes H, Wagner L, Brell JM, Cella D, Flynn P, Ramanathan RK, Crane CH, Alberts SR, Benson AB 3rd. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. *J Clin Oncol* 2011 Nov 1; 29(31):4105-12.
- ¹¹Murphy JD, Adusumilli S, Griffith KA, Ray ME, Zalupski MM, Lawrence TS, Ben-Josef E. Full-dose gemcitabine and concurrent radiotherapy for unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2007 Jul 1; 68(3): 801-808.
- ¹²Chang DT, Schellenberg D, Shen J, Kim J, Goodman KA, Fisher GA, Ford JM, Dessert T, Quon A, Koong AC. Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. *Cancer* 2009 Feb 1; 115(3): 665-672.
- ¹³Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. gastrointestinal tumor study group. *Cancer* 1987 Jun 15; 59(12): 2006-2010.
- ¹⁴Regine WF, Winter KA, Abrams RA, Safran H, Hoffman JP, Konski A, Benson AB, Macdonald JS, Kudrimoti MR, Fromm ML, Haddock MG, Schaefer P, Willett CG, Rich TA. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: A randomized controlled trial. *JAMA* 2008 Mar 5; 299(9): 1019-1026.
- ¹⁵Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA* 2010;304:1073-1081.
- ¹⁶Van Laethem JL, Hammel P, Mornex F, Azria D, Van Tienhoven G, Vergauwe P, Peeters M, Polus M, Praet M, Mauer M, Collette L, Budach V, Lutz M, Van Cutsem E, Haustermans K. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: A randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study. *J Clin Oncol* 2010 Oct 10; 28(29): 4450-4456. PMID: PMC2988636.
- ¹⁷Herman JM, Swartz MJ, Hsu CC, Winter J, Pawlik TM, Sugar E, Robinson R, Laheru DA, Jaffee E, Hruban RH, Campbell KA, Wolfgang CL, Asrari F, Donehower R, Hidalgo M, Diaz LA, Jr, Yeo C, Cameron JL, Schulick RD, Abrams R. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: Results of a large, prospectively collected database at the Johns Hopkins hospital. *J Clin Oncol* 2008 Jul 20; 26(21): 3503-3510.
- ¹⁸Zimmermann FB, Jeremic B, Lersch C, Geinitz H, Hennig M, Molls M. Dose escalation of concurrent hypofractionated radiotherapy and continuous infusion 5-FU-chemotherapy in advanced adenocarcinoma of the pancreas. *Hepatogastroenterology*. 2005 Jan-Feb; 52(61): 246-250.
- ¹⁹Ford EC, Herman J, Yorke E, Wahl RL. 18F-FDG PET/CT for image-guided and intensity-modulated radiotherapy. *J Nucl Med* 2009 Oct; 50(10): 1655-1665.
- ²⁰Schellenberg D, Quon A, Minn AY, Graves EE, Kunz P, Ford JM, Fisher GA, Goodman KA, Koong AC, Chang DT. 18Fluorodeoxyglucose PET is prognostic of progression-free and overall survival in locally advanced pancreas cancer treated with stereotactic radiotherapy. *Int J Radiat Oncol Biol Phys* 2010 Aug 1; 77(5): 1420-1425.
- ²¹Chavaudra J, Bridier A. Definition of volumes in external radiotherapy: ICRU reports 50 and 62]. *Cancer Radiother* 2001 Oct; 5(5): 472-478.
- ²²Minn AY, Schellenberg D, Maxim P, Suh Y, McKenna S, Cox B, Dieterich S, Xing L, Graves E, Goodman KA, Chang D, Koong AC. Pancreatic tumor motion on a single planning 4D-CT does not correlate with intrafraction tumor motion during treatment. *Am J Clin Oncol* 2009 Aug; 32(4):364-8.
- ²³Goldstein SD, Ford EC, Duhon M, McNutt T, Wong J, Herman JM. Use of respiratory-correlated four-dimensional computed tomography to determine acceptable treatment margins for locally advanced pancreatic adenocarcinoma. *Int J Radiat Oncol Biol Phys* 2010 Feb 1; 76(2): 597-602.
- ²⁴Feng M, Balter JM, Normolle D, Adusumilli S, Cao Y, Chenevert TL, Ben-Josef E. Characterization of pancreatic tumor motion using cine MRI: Surrogates for tumor position should be used with caution. *Int J Radiat Oncol Biol Phys* 2009 Jul 1; 74(3): 884-891. PMID: PMC2691867.
- ²⁵Spalding AC, Jee KW, Vineberg K, Jablonowski M, Fraass BA, Pan CC, Lawrence TS, Haken RK, Ben-Josef E. Potential for dose-escalation and reduction of risk in pancreatic cancer using IMRT optimization with lexicographic ordering and gEUD-based cost functions. *Med Phys* 2007 Feb; 34(2): 521-529.
- ²⁶Yovino S, Poppe M, Jabbour S, David V, Garofalo M, Pandya N, Alexander R, Hanna N, Regine WF. Intensity-modulated radiation therapy significantly improves acute gastrointestinal toxicity in pancreatic and ampullary cancers. *Int J Radiat Oncol Biol Phys* 2011 Jan 1; 79(1): 158-162.
- ²⁷Koong AC, Christofferson E, Le QT, Goodman KA, Ho A, Kuo T, Ford JM, Fisher GA, Greco R, Norton J, Yang GP. Phase II study to assess the efficacy of conventionally fractionated radiotherapy followed by a stereotactic radiosurgery boost in patients with locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2005 Oct 1; 63(2): 320-323.
- ²⁸Keall PJ, Mageras GS, Balter JM, Emery RS, Forster KM, Jiang SB, Kapatoes JM, Low DA, Murphy MJ, Murray BR, Ramsey CR, Van Herk MB, Vedam SS, Wong JW, Yorke E. The management of respiratory motion in radiation oncology report of AAPM task group 76. *Med Phys* 2006 Oct; 33(10): 3874-3900.
- ²⁹Crane CH, Beddar AS, Evans DB. The role of intraoperative radiotherapy in pancreatic cancer. *Surg Oncol Clin N Am* 2003 Oct; 12(4): 965-977.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF CHEMOTHERAPY (1 of 3)

- Systemic therapy is used in the neoadjuvant or adjuvant setting and in the management of locally advanced unresectable and metastatic disease.
- Goals of systemic therapy should be discussed with patients prior to initiation of therapy, and enrollment in a clinical trial is strongly encouraged.
- Close follow-up of patients undergoing chemotherapy is indicated.

Metastatic

- Acceptable chemotherapy combinations for patients with good performance status include:
 - ▶ FOLFIRINOX¹ (category 1) (preferred)
 - ▶ Gemcitabine + albumin-bound paclitaxel² (category 1) (preferred)
 - ▶ Gemcitabine + erlotinib³ (category 1)^a
 - ▶ Gemcitabine + capecitabine⁴
 - ▶ Gemcitabine + cisplatin⁵ (especially for patients with possible hereditary cancers)
 - ▶ Fixed-dose rate gemcitabine, docetaxel, capecitabine (GTX regimen)⁶ (category 2B)
 - ▶ Fluoropyrimidine + oxaliplatin (category 2B) (eg, 5-FU/leucovorin/oxaliplatin⁷ or CapeOx⁸)
- Acceptable monotherapy options for patients with poor performance status include:
 - ▶ Gemcitabine at 1000 mg/m² over 30 minutes, weekly for 3 weeks every 28 days (category 1).
 - ▶ Fixed-dose-rate gemcitabine (10 mg/m²/minute) may substitute for standard infusion of gemcitabine over 30 minutes (category 2B).
 - ▶ Capecitabine or continuous infusion 5-FU (category 2B)
- Second-line chemotherapy may consist of gemcitabine-based therapy for those previously treated with fluoropyrimidine-based therapy, and of fluoropyrimidine-based therapy for those previously treated with gemcitabine-based therapy.

Locally Advanced

- Depending on performance status, mono- or combination systemic chemotherapy, as noted above, may be considered as initial therapy prior to chemoradiation for appropriate patients with locally advanced, unresectable disease^b. Patients should be evaluated for recovery from hematologic and non-hematologic toxicity prior to initiation of chemoradiation. Patients who progress with metastatic disease are not candidates for chemoradiation unless required for palliative purposes.

[See Adjuvant, and Neoadjuvant PANC-G \(2 of 3\)](#)

[See References on PANC-G \(3 of 3\)](#)

^aAlthough this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.

^bBased on preliminary data from the LAP-07 trial, there is no clear survival benefit with the addition of conventional chemoradiation following gemcitabine monotherapy. (Hammel P, Huguet F, van Laethem J-L, et al: Comparison of chemoradiotherapy and chemotherapy in patients with a locally advanced pancreatic cancer controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study. 2013 ASCO Annual Meeting. Abstract LBA4003.)

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PRINCIPLES OF CHEMOTHERAPY (2 of 3)

Adjuvant

- The CONKO 001 trial demonstrated significant improvements in disease-free survival and overall survival with use of postoperative gemcitabine as adjuvant chemotherapy versus observation in resectable pancreatic adenocarcinoma.⁹
- ESPAC-3 study results showed no significant difference in overall survival between 5-FU/leucovorin versus gemcitabine following surgery. When the groups receiving adjuvant 5-FU/leucovorin and adjuvant gemcitabine were compared, median survival was 23.0 months and 23.6 months, respectively.¹⁰
- The use of gemcitabine-based chemotherapy is frequently combined, sequentially, with 5-FU-based chemoradiotherapy.
- No significant differences were observed in the RTOG 97-04 study comparing pre- and post-chemoradiation 5-FU with pre- and post-chemoradiation gemcitabine for postoperative adjuvant treatment.¹¹
- For patients with good performance status who relapse after receiving adjuvant therapy, FOLFIRINOX or gemcitabine + albumin-bound paclitaxel are options depending on the length of time since completion of adjuvant therapy.

Neoadjuvant

- There is limited evidence to recommend specific neoadjuvant regimens off-study, and practices vary with regard to the use of chemotherapy and chemoradiation. Acceptable regimens include FOLFIRINOX or gemcitabine + albumin-bound paclitaxel. Subsequent chemoradiation is sometimes included. Most NCCN Member Institutions prefer neoadjuvant therapy at a high-volume center.

[See Metastatic and Locally Advanced PANC-G \(1 of 3\)](#)

[See References on PANC-G \(3 of 3\)](#)

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



PRINCIPLES OF CHEMOTHERAPY (3 of 3)

References

- ¹Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817-1825.
- ²Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; 369:1691-1703.
- ³Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer. A phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007;25:1960-1966.
- ⁴Cunningham D, Chau I, Stocken D D, et al. Phase III randomized comparison of gemcitabine (GEM) versus gemcitabine plus capecitabine (GEM-CAP) in patients with advanced pancreatic cancer. *J Clin Oncol* 2009; 27:5513-5518.
- ⁵Oliver GR, Sugar E, Laheru D, et al. Family history of cancer and sensitivity to platinum chemotherapy in pancreatic adenocarcinoma [abstract]. Presented at: 2010 ASCO Gastrointestinal Cancers Symposium; January 22-24, 2010; Orlando, Florida. Abstract 180.
- ⁶Fine RL, Fogelman DR, Schreiber SM, et al. The gemcitabine, docetaxel, and capecitabine (GTX) regimen for metastatic pancreatic cancer: a retrospective analysis. *Cancer Chemother Pharmacol* 2008;61:167-175.
- ⁷Pelzer U, Schwaner I, Stieler J, et al. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. *Eur J Cancer* 2011;47:1676-1681.
- ⁸Xiong HQ, Varadhachary GR, Blais JC, et al. A phase II trial of oxaliplatin plus capecitabine (xelox) as second-line therapy for patients with advanced pancreatic cancer. *Cancer* 2008; 113:2046-2052.
- ⁹Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant Chemotherapy With Gemcitabine and Long-term Outcomes Among Patients With Resected Pancreatic Cancer: The CONKO-001 Randomized Trial. *JAMA* 2013;310(14):1473-1481.
- ¹⁰Neoptolemos J, Buchler M, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA* 2010;304:1073-1081.
- ¹¹Regine, WF Winter KA, Abrams RA et al. Fluorouracil vs. gemcitabine chemotherapy before and after fluorouracil-based chemoradiation after resection of pancreatic adenocarcinoma. A randomized controlled trial. *JAMA* 2008; 299:1019-1026.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Table 1

American Joint Committee on Cancer (AJCC) TNM Staging of Pancreatic Cancer (2010)

Because only a few patients with pancreatic cancer undergo surgical resection of the pancreas (and adjacent lymph nodes), a single TNM classification must apply to both clinical and pathologic staging.

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ*
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

* This also includes the “PanInIII” classification.

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant Metastases (M)

M0	No distant metastases
M1	Distant metastasis

Stage Grouping

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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Overview

During the year 2014 in the United States, an estimated 46,420 people will be diagnosed with pancreatic cancer, and approximately 39,590 people will die of pancreatic cancer.¹ This disease is the fourth most common cause of cancer-related death among U.S. men (after lung, prostate, and colorectal cancer) and women (after lung, breast, and colorectal cancer).¹ Its peak incidence occurs in the seventh and eighth decades of life.¹ Although incidence is roughly equal in both sexes, African Americans have a higher incidence of pancreatic cancer than white Americans.^{2,3} Furthermore, the incidence of pancreatic cancer in the United States increased from 1999 to 2008, possibly because of the increasing prevalence of obesity, an aging population, and other unknown factors.³⁻⁵ Mortality rates have remained largely unchanged.^{6,7}

In these NCCN Guidelines for Pancreatic Adenocarcinoma, the diagnosis and management of adenocarcinomas of the exocrine pancreas are discussed; neuroendocrine tumors are not included (please see the NCCN Guidelines for Neuroendocrine Tumors, available at www.NCCN.org). These NCCN Guidelines are intended to assist with clinical decision-making, but they cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the panel members during the process of developing and updating these guidelines. A 5% rule (omitting clinical scenarios that comprise less than 5% of all cases) was used to eliminate uncommon clinical occurrences or conditions from these guidelines. A recent study of 3706 patients treated for pancreatic cancer in large California hospitals showed that compliance with these NCCN Guidelines for Pancreatic Adenocarcinoma, defined very permissively, improves survival.⁸

As an overall guiding principle of these guidelines, the panel believes that decisions about diagnostic management and resectability of pancreatic cancer should involve multidisciplinary consultation at high-volume centers with use of appropriate imaging studies. In addition, the panel believes that increasing participation in clinical trials (only 4.6% of patients enroll in a pancreatic cancer trial⁹) is critical to making progress in this disease. Thus, the panel unanimously endorses participation in a clinical trial over standard or accepted therapy.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Pancreatic Adenocarcinoma, an electronic search of the PubMed database was performed to obtain key literature in the field of pancreatic cancer published between July 28, 2013 and July 28, 2014, using the following search terms: (pancreatic cancer) OR (pancreatic adenocarcinoma) OR (pancreas adenocarcinoma) OR (pancreas cancer). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.¹⁰

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Practice Guideline; Guidelines; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 152 citations, and their potential relevance was examined. The data from key PubMed articles and articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting

abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (www.NCCN.org).

Risk Factors and Genetic Predisposition

Although the increase in risk is small, pancreatic cancer is firmly linked to cigarette smoking.¹¹⁻¹⁶ An increased body mass index (BMI) is also associated with an increased risk for pancreatic cancer.¹⁷⁻²⁰ There is also some evidence that increased consumption of red/processed meat and dairy products is associated with an elevation in pancreatic cancer risk,^{21,22} although other studies have failed to identify dietary risk factors for the disease.^{15,23,24} Occupational exposure to chemicals such as beta-naphthylamine and benzidine is associated with increased risk for pancreatic cancer,²⁵ as is heavy alcohol consumption.^{11,13,17,26} Recent data also suggest that low plasma 25-hydroxyvitamin D levels may increase the risk for pancreatic cancer.²⁷ Chronic pancreatitis has also been identified as a risk factor for pancreatic cancer,²⁸⁻³¹ with one study demonstrating a 7.2-fold increased risk for pancreatic cancer for patients with a history of pancreatitis.³² Overall, further epidemiologic studies involving careful evaluation of these possible risk factors with adjustments for potential confounders are needed to clarify their impact on pancreatic cancer risk.

Diabetes and Pancreatic Cancer

The association between diabetes mellitus and pancreatic cancer is particularly complicated. Numerous studies have shown an association between new-onset non-insulin-dependent diabetes and the development of pancreatic cancer,³³⁻³⁷ especially in those who are

elderly, have a lower BMI, experience weight loss, or do not have a family history of diabetes.³⁸ In these short-onset cases of diabetes diagnosed prior to pancreatic cancer diagnoses, diabetes is thought to be caused by the cancer, although the physiologic basis for this effect is not yet completely understood.³⁹ A population-based study of 2122 patients with diabetes found that approximately 1% of patients diagnosed with diabetes who are age 50 years or younger will be diagnosed with pancreatic cancer within 3 years.³³

Long-term diabetes, on the other hand, appears to be a risk factor for pancreatic cancer, as some studies have shown an association of pancreatic cancer with diabetes of 2- to 8-year duration.⁴⁰ However, certain risk factors such as obesity, associated with both diabetes and pancreatic cancer, may confound these analyses.⁴¹ Furthermore, the use of diabetic medications has been reported to alter pancreatic cancer risk.⁴² The use of insulin or sulfonylureas has been found to be associated with an increased risk for pancreatic cancer.⁴³⁻⁴⁵ On the other hand, metformin may be associated with a reduced risk for pancreatic and other cancers.⁴³⁻⁴⁸

In addition, diabetes and diabetic medication may affect outcomes in patients with pancreatic cancer. Metformin use has been reported to result in higher pancreatic cancer survival in diabetics. A retrospective analysis of 302 patients with pancreatic cancer and diabetes treated at The University of Texas MD Anderson Cancer Center found that metformin use was associated with increased survival at 2 years (30.1% vs. 15.4%; $P = .004$) and increased overall survival (OS, 15.2 months vs. 11.1 months; $P = .009$).⁴⁹ The OS difference was significant only in patients without distant metastases and remained significant when insulin users were excluded. In contrast, data from a recent meta-analysis of >38,000 patients show that those with pancreatic cancer and diabetes have a significantly lower OS than those without diabetes (14.4

vs. 21.7 months; $P < 0.001$).³⁶ A similar result was seen in a prospective cohort study, in which the survival of 504 patients with and without diabetes who developed pancreatic cancer in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial was compared.⁵⁰ After multivariable-adjustment, mortality was significantly higher in participants with diabetes compared to those without (HR, 1.52; 95% CI, 1.14–2.04; $P < .01$).

Genetic Predisposition

Pancreatic cancer is thought to have a familial component in approximately 10% of cases, and familial excess of pancreatic cancer is associated with high risk.^{15,51–54} The genetic basis of this inherited predisposition is not known in most cases; however, some familial cancer syndromes are associated with an increased risk for pancreatic cancer (see *Table 1*, below).

Germline mutations in the *STK11* gene result in Peutz-Jeghers syndrome, in which individuals have gastrointestinal polyps and a highly elevated risk for colorectal cancer.^{55–57} These individuals also have a highly elevated risk for developing pancreatic cancer, reported to be increased by as much as 132-fold.^{58,59} Furthermore, *STK11* undergoes somatic mutation in approximately 5% of pancreatic cancers.⁶⁰

As with non-hereditary forms of pancreatitis, familial pancreatitis is also associated with an increased risk for pancreatic cancer.⁶¹ Several genes are associated with the familial form of pancreatitis, including *PRSS1*, *SPINK1*, and *CFTR*.⁶² The increased risk for the development of pancreatic cancer in these individuals is estimated to be 26-fold to as high as 87-fold.^{29,63–65}

Familial Malignant Melanoma syndrome (also known as Melanoma-Pancreatic Cancer syndrome or Familial Atypical Multiple Mole

Melanoma syndrome [FAMMM]) is caused by germline mutation of the *CDKN2A* (p16INK4a/p14ARF) gene.⁶⁶ This syndrome is associated with a 20-fold to 47-fold increased risk for pancreatic cancer.^{67,68} In addition, patients with Melanoma-Pancreatic Cancer syndrome may experience an earlier onset of pancreatic cancer than the general population.⁶⁹ In an unselected series of 225 patients with pancreatic cancer in Italy, 5.7% had mutations in *CDKN2A*.⁷⁰

Lynch syndrome is the most common form of genetically determined colorectal cancer predisposition and is caused by germline mutations in DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*).^{71–76} Patients with Lynch syndrome also have an estimated 9- to 11-fold elevated risk for pancreatic cancer.^{77,78}

An excess of pancreatic cancer is also seen in families with hereditary Breast-Ovarian Cancer syndrome, harboring *BRCA1* and *BRCA2* (breast cancer susceptibility gene-1 and -2) mutations, although the link with *BRCA2* is better established.^{79–84} In a study of 187 Ashkenazi Jewish patients who had resections for pancreatic cancer, mutations in *BRCA1* and *BRCA2* were identified in 5.5% of patients.⁸¹ Other studies of unselected patients with pancreatic cancer have detected *BRCA* mutations at a frequency of 4% to 7%.⁸⁵ The risk of pancreatic cancer is elevated 2- to 6-fold in these patients, and the age of onset is younger than average in the general population.^{79,83,84}

BRCA1 and *BRCA2* are involved in the Fanconi DNA anemia/BRCA pathway. This pathway is responsible for the repair of DNA interstrand cross-links, and particular mutations in other Fanconi anemia/BRCA pathway genes, including in *PALB2*, *FANCC*, and *FANCG*, have also been identified as increasing pancreatic cancer susceptibility.^{86–88} Additionally, whole-genome sequencing recently allowed for the identification of germline mutations in *ATM*, a DNA damage response

gene, in 2 kindreds with familial pancreatic cancer.⁸⁹ Further analyses then revealed *ATM* mutations in 4 of 166 individuals with familial pancreatic cancer.

As many as 80% of patients with a family history of pancreatic cancer have no known genetic cause.⁵¹ A prospective registry-based study of 5179 individuals from 838 kindreds found that having just 1 first-degree relative with pancreatic cancer raises the risk for pancreatic cancer by 4.6-fold, whereas having 2 affected first-degree relatives raises the risk by about 6.4-fold.⁹⁰

The panel emphasizes the importance of taking a thorough family history when seeing a new patient with pancreatic cancer. In particular, a family history of pancreatitis, melanoma, and cancers of the pancreas, colorectum, breast, and ovaries should be noted. A free online pancreatic cancer risk prediction tool, called PancPRO, is available and may help determine risk.⁵⁴ If a cancer syndrome is identified, at-risk relatives should be offered genetic counseling. With or without a known syndrome, individuals with a suspicious family history should be advised on risk-reducing strategies including smoking cessation and weight loss. In addition, the possibility of screening for pancreatic (see below) and other cancers should be discussed.

Premalignant Tumors of the Pancreas

Mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are cystic lesions that can be small and asymptomatic and are often discovered incidentally; MCNs have an ovarian-like stroma.⁹¹⁻⁹³ IPMNs can occur in the main duct and/or in the branch ducts. Lesions involving the main duct have a higher malignant potential than those in the branches, with the risk of malignancy at around 62%.⁹⁴ The risk of malignancy in MCNs is <15%.⁹⁴

An international group of experts has established guidelines for the management of pancreatic IPMNs and MCNs,⁹⁴ as has a European group.⁹⁵ The international group strongly recommends resection in fit patients with main duct IPMNs.⁹⁴ For branch-duct IPMNs, surveillance is considered an appropriate option in older or unfit patients or for cysts lacking suspicious features. Branch-duct IPMNs that are ≥ 10 mm, have an enhancing solid component, or are in the head of the pancreas causing obstructive jaundice should be considered for resection.⁹⁴ Patients with resected IPMNs are followed with imaging studies to identify recurrences. For MCNs, the international group recommends resection for all fit patients, and recurrences are not observed.⁹⁴ The European group gives similar recommendations.⁹⁵

Pancreatic Cancer Screening

Asymptomatic individuals at high risk for pancreatic cancer (ie, those with first-degree relatives with pancreatic cancer) were assessed using endoscopic ultrasound (EUS) in the Cancer of the Pancreas Screening 2 (CAPS2) project.⁹⁶ Preinvasive pancreatic neoplasms were detected in 10% of high-risk patients, suggesting that EUS may have a promising role in screening high-risk patients. The CAPS Consortium recently reported results of their CAPS3 study, in which 225 asymptomatic high-risk individuals were independently (in a blinded manner) screened once with CT, MRI, and EUS.⁹⁷ In this study, 42% of individuals were found to have an abnormality; 5 individuals underwent surgical interventions, 3 of whom had high-grade dysplasia in small IPMNs and intraepithelial neoplasias. When results of the 3 screening modalities were compared, EUS detected abnormalities in 42% of individuals, versus 33% and 11% for MRI and CT, respectively.

Interestingly, results from a prospective cohort study that followed high-risk individuals for an average of 4.2 years with annual MRI were

recently published.⁹⁸ Although 32% of 262 participants were found to have pancreatic abnormalities and some IPMNs and intraepithelial neoplasias were resected, 3 patients developed pancreatic adenocarcinoma (2 metastatic, 1 recurrent 30 months post-resection) despite screening. These results could be due to rapid malignant progression, but they are more likely a result of inadequate imaging by MRI.

The diagnostic yield of pancreatic cancer screening with EUS in asymptomatic individuals at high risk for familial disease was also investigated in the Netherlands,⁹⁹ while a German study used EUS plus MRI/magnetic resonance cholangiopancreatography (MRCP) in a similar high-risk population.¹⁰⁰ Although results from these trials seem promising overall, the malignant potential of some preinvasive pancreatic lesions and the impact of screening on survival are presently unclear. Results suggest that MRI/MRCP may be a useful adjunct or a noninvasive alternative to EUS for pancreatic cancer screening.

Newer screening methods to identify patients with early pancreatic cancer rather than those with preinvasive lesions may prove to be beneficial in the future. Examples of techniques being investigated are microRNA biomarkers in whole blood and serum metabolism profiling.¹⁰¹⁻¹⁰⁴ In addition, circulating cell-free DNA is being investigated as a possible biomarker for screening. One study showed that methylation patterns in cell-free plasma DNA can differentiate between pancreatitis and pancreatic cancer with a sensitivity of 91.2% and specificity of 90.8%.¹⁰⁵ In addition, CA 19-9 levels may be elevated in patients up to 2 years before a pancreatic cancer diagnosis, indicating that CA 19-9 has potential as a biomarker for screening high-risk patients.¹⁰⁶

An international CAPS Consortium summit with 49 multidisciplinary experts was held in 2011 to develop consensus guidelines for pancreatic cancer screening.¹⁰⁷ The group recommends screening with EUS and/or MRI/MRCP for high-risk individuals, defined as first-degree relatives of patients with pancreatic cancer from familial kindreds; carriers of *p16* or *BRCA2* mutations with an affected first-degree relative; patients with Peutz-Jeghers syndrome; and patients with Lynch syndrome and an affected first-degree relative with pancreatic cancer. The group also concluded that more evidence is needed regarding optimal management of patients with detected lesions, the age to begin screening, and screening intervals.

Diagnosis and Staging

Ductal adenocarcinoma and its variants account for over 90% of pancreatic malignancies. The presenting symptoms of this disease can include weight loss, jaundice, floating stools, pain, dyspepsia, nausea, and depression; however, no early warning signs of pancreatic cancer have been established. As previously noted, sudden onset of adult type 2 diabetes in patients 50 years or older may be linked to a new diagnosis of pancreatic cancer; patients with long-standing diabetes may also develop pancreatic cancer (see *Diabetes and Pancreatic Cancer*, above). Thus, pancreatic carcinoma should be considered in diabetic patients with unusual manifestations, such as abdominal symptoms and continuous weight loss.

Unlike many other cancers, imaging is the primary means through which the stage of pancreatic cancer is determined. High-quality multi-phase imaging can help to preoperatively distinguish between patients eligible for resection with curative intent and those with unresectable disease. The criteria for defining resectable disease favor specificity over sensitivity to avoid denying surgery to patients with a potentially

resectable tumor.¹⁰⁸ All patients for whom there is clinical suspicion of pancreatic cancer or evidence of a dilated duct (stricture) should therefore undergo initial evaluation by CT performed according to a dedicated pancreas protocol.¹⁰⁹ In addition, the panel recommends imaging after neoadjuvant treatment to provide adequate staging and assessment of resectability status. Subsequent decisions regarding diagnostic management and resectability should involve multidisciplinary consultation, with use of appropriate studies to evaluate the extent of disease. The panel recommends that a multidisciplinary review ideally involve expertise from surgery, diagnostic imaging, interventional endoscopy, medical oncology, radiation oncology, and pathology.

The AJCC has developed staging criteria for adenocarcinoma of the pancreas that follow the tumor/node/metastasis (TNM) system.¹¹⁰ Although the TNM staging criteria for pancreatic cancer in the 7th edition of the AJCC Cancer Staging Manual have taken into account the fact that tumors of the pancreas are evaluated preoperatively by CT or MRI to determine resectability status, these staging criteria also include information that can be determined only through postsurgical pathologic evaluation of resected tumor.^{110,111} Recent validation of concordance between AJCC stage and OS has been provided through evaluation of 121,713 patients with pancreatic adenocarcinoma included in the National Cancer Data Base (NCDB).¹¹¹

For clinical purposes, however, most NCCN Member Institutions use a clinical classification system based mainly on results of presurgical imaging studies. Following staging by pancreatic protocol CT (and EUS and/or MRI/MRCP or endoscopic retrograde cholangiopancreatography [ERCP] in some cases), liver function tests, and chest imaging, disease is classified as: 1) resectable; 2) borderline resectable (ie, tumors that are involved with nearby structures so as to be neither clearly

resectable nor clearly unresectable with a high chance of an R1 resection); 3) locally advanced unresectable (ie, tumors that are involved with nearby structures to an extent that renders them unresectable despite the absence of evidence of metastatic disease); or 4) disseminated, and this system is used throughout the guidelines. See *Criteria for Resection* below for more detailed definitions.

Imaging Evaluations

Pancreatic Protocol CT and MRI

Multi-detector CT angiography, performed by acquiring thin, preferably sub-millimeter, axial sections using a dual-phase pancreatic protocol, with images obtained in the pancreatic and portal venous phase of contrast enhancement, is the preferred imaging tool for dedicated pancreatic imaging. Scan coverage can be extended to cover the chest and pelvis for complete staging as per institutional preferences. Multiplanar reconstruction is preferred as it allows precise visualization of the relationship of the primary tumor to the mesenteric vasculature as well as detection of subcentimeter metastatic deposits.^{108,109,112} Studies have shown that 70% to 85% of patients determined by CT imaging to have resectable tumors were able to undergo resection.^{108,113-117} However, the sensitivity of CT for small hepatic and peritoneal metastases is limited.

The difference in contrast enhancement between the parenchyma and adenocarcinoma is highest during the late arterial phase, thereby providing a clear distinction between a hypodense lesion in the pancreas and the rest of the organ. A multi-phasic pancreatic protocol also allows for selective visualization of important arterial (eg, celiac axis, superior mesenteric artery [SMA], peripancreatic arteries) and venous structures (eg, superior mesenteric vein [SMV], splenic vein, portal vein [PV]), thereby providing an assessment of vascular invasion by the tumor. All of this information can improve the prediction of

resectability. Software allowing for 3-D reconstruction of imaging data can provide additional valuable information on the anatomic relationship between the pancreatic tumor and the surrounding blood vessels and organs, and multiplanar reconstruction is preferred. However, further development of this technology may be needed before it is routinely integrated into clinical practice.¹¹⁶

Patients commonly present to the oncologist with a non-pancreas protocol CT already performed. The panel feels that if the CT scan is of high quality, it can be sufficient. If not, a pancreas protocol CT is recommended. Such selective reimaging was shown to change the staging and management of patients with pancreatic adenocarcinoma in 56% of cases retrospectively reviewed at one institution.¹¹⁸

Pancreas protocol MRI can be a helpful adjunct to CT in the staging of pancreatic cancer, particularly for characterization of CT-indeterminate liver lesions and when suspected pancreatic tumors are not visible on CT or in cases of contrast allergy.^{119,120}

Recently, a multidisciplinary expert consensus group defined standardized language for the reporting of imaging results.¹⁰⁹ Such uniform reporting can help improve the accuracy and consistency of staging to determine optimal treatment strategies for individual patients and can allow cross-study and cross-institutional comparisons for research purposes. Use of the template also ensures a complete assessment and reporting of all imaging criteria essential for optimal staging and can therefore aid in determining optimal management. The use of the radiology staging reporting template is thus preferred by the panel.

Endoscopic Ultrasound

NCCN Member Institutions vary in the use of additional staging technologies, such as EUS. The role of EUS in staging is felt to be complementary to CT, providing additional information for patients whose initial scans show no lesion or whose lesions have questionable involvement of blood vessels or lymph nodes.¹²¹⁻¹²⁴ In particular, EUS may provide assessment of certain types of vascular invasion.^{125,126} It is the consensus of the panel that while the accuracy of EUS in assessing the involvement of certain veins (eg, PV) is high, this technique is less accurate in imaging tumor invasion of the SMA.¹²⁷ Therefore, EUS is not recommended as a routine staging tool.

EUS is also used to discriminate between benign and malignant strictures or stenosis, because severe stenosis and marked proximal dilatation most often indicate malignancy.¹²⁸ EUS can also be used to evaluate periampullary masses, separating invasive from noninvasive lesions. In addition, EUS plays a role in better characterizing cystic pancreatic lesions due to the ability to aspirate the cyst contents for cytologic, biochemical, and molecular analysis. On EUS, malignant cystic lesions may present as a hypoechoic cystic/solid mass or as a complex cyst, and they are frequently associated with a dilated main pancreatic duct. Some therapeutic interventions can also be done with EUS (eg, celiac neurolysis, removal of ascites). Because this procedure is operator dependent, some divergence in use may occur because of differing technical capabilities and available expertise.

Endoscopic Retrograde Cholangiopancreatography and MRI/Magnetic Resonance Cholangiopancreatography

ERCP is a technique that combines endoscopic and fluoroscopic procedures and is generally limited to therapeutic interventions.¹²⁹ In the guidelines, ERCP with duct brushing cytology is recommended as clinically indicated for patients without a mass in the pancreas and

without evidence of metastatic disease who require biliary decompression and who undergo additional imaging with EUS to help establish a diagnosis.¹³⁰ Thus from a therapeutic standpoint, ERCP allows for stent placement and can be used to palliate biliary obstruction when surgery is not elected or if surgery must be delayed.

MRI/MRCP is considered to be equivalent to EUS/ERCP in the diagnostic setting; brushings can be obtained with either. MRI/MRCP can also be performed with secretin to increase secretion of pancreatic juices from the proximal pancreas for better delineation of a pancreatic duct that has a subtle stricture.¹³¹

PET/CT

The utility of PET/CT for upstaging patients with pancreatic cancer has also been evaluated. In a retrospective study, the use of PET/CT following a standard CT protocol showed increased sensitivity for detection of metastatic disease when compared with the standard CT protocol or PET/CT alone.¹³² The sensitivity of detecting metastatic disease for PET/CT alone, standard CT alone, and the combination of PET/CT and standard CT were 61%, 57%, and 87%, respectively. In this study, the clinical management of 11% of patients with invasive pancreatic cancer was changed as a result of PET/CT findings. Nevertheless, the role of PET/CT in this setting is evolving and has not yet been established.^{133,134} PET/CT is not a substitute for high-quality contrast-enhanced CT, although it can be considered as an adjunct to a formal pancreatic CT protocol in high-risk patients. Indicators of high risk for metastatic disease may include borderline resectable disease, markedly elevated carbohydrate antigen (CA) 19-9, large primary tumors, large regional lymph nodes, and patients who are very symptomatic.

Laparoscopy

Laparoscopy is another potentially valuable diagnostic tool for staging; it can identify peritoneal, capsular, or serosal implants or studding of metastatic tumor on the liver that may be missed even with the use of a pancreatic CT protocol.¹³⁵⁻¹³⁷ The yield of laparoscopy is dependent on the quality of preoperative imaging and the likelihood of metastatic disease. A key goal is to avoid unnecessary laparotomy, which can be accomplished in an estimated 23% of patients in whom curative intent surgery is planned,¹³⁶ although routine use of staging laparoscopy is controversial. The panel does not consider staging laparoscopy to be a substitute for poor-quality preoperative imaging.

Some evidence provides support for a selective approach to staging laparoscopy (ie, it is performed if the presence of occult metastatic disease is suggested by high-quality imaging or certain clinical indicators).¹³⁸ For example, preoperative serum CA 19-9 levels >100 U/mL or >215 U/mL (see discussion of *Biomarkers*, below) have been associated with a greater likelihood of advanced disease and an increased probability of a positive finding on staging laparoscopy.^{139,140} In a recent prospective review of 838 patients who were diagnosed with resectable pancreatic tumors on imaging evaluation between 1999 and 2005, 14% were found to have unresectable disease (21% yield if only pancreatic adenocarcinoma was considered) following subsequent laparoscopy.¹⁴¹ Characteristics associated with an increased laparoscopic yield of unresectable disease include the location of the tumor, tumor histology, the presence of weight loss and jaundice, and the facility conducting the imaging evaluation.

Diagnostic staging laparoscopy to rule out metastases not detected on imaging (especially for patients with body and tail lesions) is used routinely in some NCCN Member Institutions prior to surgery or

chemoradiation, or selectively in patients who are at higher risk for disseminated disease (ie, borderline resectable disease; markedly elevated CA 19-9; large primary tumors; large regional lymph nodes; highly symptomatic). Thus the panel believes that staging laparoscopy can be considered for patients staged with resectable pancreatic cancer who are considered to be at increased risk for disseminated disease and for patients with borderline resectable disease prior to administration of neoadjuvant therapy. The panel considers positive cytology from washings obtained at laparoscopy or laparotomy to be equivalent to M1 disease.¹⁴²

Biopsy

Although a pathologic diagnosis is not required before surgery, it is necessary before administration of neoadjuvant therapy and for patients staged with locally advanced, unresectable pancreatic cancer or metastatic disease. A pathologic diagnosis of adenocarcinoma of the pancreas is often made using fine-needle aspiration (FNA) biopsy with either EUS guidance (preferred) or CT. EUS-FNA is preferable to CT-guided FNA in patients with resectable disease because of better diagnostic yield, safety, and potentially lower risk of peritoneal seeding with EUS-FNA when compared with the percutaneous approach.¹⁴³⁻¹⁴⁵ Additional risks of CT-directed FNA biopsy include the potential for greater bleeding and infection because of the need to traverse vessels and bowel. EUS-FNA also gives the benefit of additional staging information at the time of biopsy.

EUS-FNA is highly accurate and reliable for determining malignancy. A recent retrospective analysis of 317 patients with EUS-FNA results from 2 institutions found that 97% of cases deemed malignant were in fact malignant on clinical follow-up.¹⁴⁶ In contrast, 13% of cases that were classified as benign were actually malignant. In rare cases when an

EUS-FNA cannot be obtained from a borderline resectable or unresectable patient, other acceptable methods of biopsy exist. For instance, intraductal biopsies can be obtained via endoscopic cholangioscopy.¹⁴⁷ A percutaneous approach¹⁴⁴ or a laparoscopic biopsy¹⁴⁸ are other alternatives. Pancreatic ductal brushings or biopsies can also be obtained at the time of ERCP, often revealing malignant cytology consistent with pancreatic adenocarcinoma.

If a biopsy does not confirm malignancy, at least 1 repeat biopsy should be performed; EUS-FNA with or without a core biopsy at a center with multidisciplinary expertise is preferred. Alternative diagnoses including autoimmune pancreatitis should be considered (see *Differential Diagnoses*, below). A positive biopsy is required before administration of chemotherapy. However, it is important to reiterate that biopsy proof of malignancy is not required before surgical resection for clearly resectable or borderline resectable patients and that a nondiagnostic biopsy should not delay surgical resection when the clinical suspicion for pancreatic cancer is high. The NCCN Pancreatic Adenocarcinoma Panel strongly recommends that all diagnostic and surgical management decisions involve multidisciplinary consultation.

Evolving changes in molecular analyses of pancreatic cancer have led some institutions to attempt to procure additional tumor-rich, formalin-fixed, paraffin-embedded tissue to bank for future genomic studies. Several methods can be used to obtain such samples, including core biopsy, but the panel believes that core biopsies should not replace EUS-FNA, but rather can be done in addition to EUS-FNA.

Differential Diagnoses

Chronic pancreatitis and other benign conditions are possible differential diagnoses of patients suspected of having pancreatic cancer.¹⁴⁹⁻¹⁵³ Autoimmune pancreatitis, a rare form of chronic

pancreatitis also known as lymphoplasmacytic sclerosing pancreatitis, is a heterogeneous disease that can present with clinical and radiologic characteristics of pancreatic cancer, such as jaundice, weight loss, an elevated CA 19-9 level, and the presence of diffuse pancreatic enlargement, a pancreatic ductal stricture, or a focal pancreatic mass.^{151,154-156} The classic appearance of the pancreas on abdominal CT in patients with diffuse pancreatic involvement is a sausage-shaped enlargement of the organ with a capsule-like peripheral rim surrounding the pancreas, although focal enlargement of the pancreas is observed in some cases.¹⁵⁵ Cardinal histologic features of autoimmune pancreatitis include prominent lymphocytic infiltration of the pancreatic parenchyma with associated fibrosis.

In addition, fine-needle aspirates can be misinterpreted as malignant or suspicious for malignancies.^{157,158} As a benign disease that can be effectively treated with corticosteroids, autoimmune pancreatitis must be distinguished from pancreatic cancer to avoid unnecessary surgery and prevent delay in the initiation of appropriate treatment.¹⁵⁷⁻¹⁶⁰

The finding of increased serum immunoglobulin (Ig) G levels is supportive of a diagnosis of autoimmune pancreatitis, although an elevated level of serum IgG4 specifically is the most sensitive and specific laboratory indicator.¹⁶¹ A recent study found that IgG4 levels of >1.0 g/L combined with CA 19-9 levels of <74 U/mL distinguished patients with autoimmune pancreatitis from those with adenocarcinoma with 94% sensitivity and 100% specificity.¹⁶² Jaundiced patients with locally advanced disease should be reviewed for autoimmune pancreatitis, and IgG4 levels should be assessed.

Autoimmune pancreatitis can, however, be negative for IgG4, thus closely mimicking pancreatic adenocarcinoma when there is a large pancreatic mass. For patients with borderline resectable disease and

cancer not confirmed after 2 or 3 biopsies, a second opinion is recommended. Alternative diagnoses should be considered, especially autoimmune pancreatitis, and a short course of steroid treatment may be an appropriate first approach. If no response is seen, the patient should undergo laparotomy for removal of the mass.

Biomarkers

Many tumor-associated antigens have been studied in connection with pancreatic adenocarcinoma, including carcinoembryonic antigen (CEA), pancreatic anti-oncofetal antigen, tissue polypeptide antigen, CA 125, and CA 19-9. The panel recognizes the importance of identifying biomarkers to personalize therapy in this difficult disease, and they emphasize the need for collection and sharing of tissue to help accelerate the discovery of predictive and prognostic biomarkers (see *Future Clinical Trials: Recommendations for Design*, below).

CA 19-9

The best validated and most clinically useful biomarker is CA 19-9, a sialylated Lewis A blood group antigen. CA 19-9 is commonly expressed and shed in pancreatic and hepatobiliary disease and in many malignancies; thus, it is not tumor-specific. However, the degree of increase in CA 19-9 levels may be useful in differentiating pancreatic adenocarcinoma from inflammatory conditions of the pancreas (see *Differential Diagnoses*, below).¹⁶³ CA 19-9 has potential uses in diagnosis, in screening, in staging, in determining resectability, as a prognostic marker after resection, and as a predictive marker for response to chemotherapy.¹⁶⁴

CA 19-9 is a good diagnostic marker, with sensitivity of 79% to 81% and specificity of 82% to 90% in symptomatic patients, but its low positive predictive value makes it a poor biomarker for screening.¹⁶⁵

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Pancreatic Adenocarcinoma

Preoperative CA 19-9 levels correlate with both AJCC staging and resectability and thus can provide additional information for staging and determining resectability, along with information from imaging, laparoscopy, and biopsy.¹⁶⁶⁻¹⁶⁸

CA 19-9 also seems to have value as a prognostic and a predictive marker for pancreatic cancer in various settings. In resectable disease, for instance, low postoperative serum CA 19-9 levels or a serial decrease in CA 19-9 levels following surgery have been found to be prognostic for survival for patients undergoing resection.^{165,166,168-174} In a prospective study of patients undergoing surgery with curative intent, median survival for the group of patients with post-resectional CA 19-9 levels of <180 U/mL was significantly higher compared with the group with higher levels of CA 19-9 following surgery (HR, 3.53; $P < .0001$).¹⁷⁰

Also in the resectable setting, data from an analysis of 260 consecutive patients support the predictive role of postoperative CA 19-9 levels for benefit of adjuvant therapy.¹⁷³ Among patients with CA 19-9 levels of <90 U/mL, those who received adjuvant therapy (mostly gemcitabine-based) had a longer disease-free survival (DFS) than those who did not (26.0 months vs. 16.7 months; $P = .011$). In contrast, patients with higher CA 19-9 levels did not appear to benefit from adjuvant therapy, with DFS of 16.2 months and 9.0 months for those receiving or not receiving adjuvant therapy, respectively ($P = .719$). In this same study, the 11 patients with post-adjuvant therapy CA 19-9 levels <37 U/mL did not die of pancreatic cancer, while the 8 patients with increased CA 19-9 levels post-adjuvant therapy had a median DFS of 19.6 months, suggesting a possible prognostic benefit of post-adjuvant therapy CA 19-9 levels in this setting.

In the neoadjuvant/borderline resectable setting, a recent study of 141 patients treated at MD Anderson Cancer Center found that post-

treatment CA 19-9 levels were a good prognostic marker in patients receiving neoadjuvant therapy with or without subsequent resection.¹⁷⁵ This study found that a normalization of CA 19-9 to <40 U/mL was associated with improvements in OS in non-resected (15 months vs. 11 months; $P = .02$) and resected (38 months vs. 26 months; $P = .02$) patients.

In the advanced disease setting, data support the role of CA 19-9 as a prognostic marker.^{169,176,177} In a prospective study of patients with advanced pancreatic cancer, pretreatment CA 19-9 serum levels were shown to be an independent prognostic factor for survival.¹⁷⁶ In addition, the change in CA 19-9 levels during chemotherapy in patients with advanced disease has been shown to be useful for evaluating the benefit of treatment, although the data are not entirely consistent.¹⁷⁶⁻¹⁸¹ For example, a recent study that pooled individual patients' data from 6 prospective trials found that a decline in CA 19-9 levels from baseline to after surgery and 2 rounds of adjuvant therapy were associated with a better outcome.¹⁶⁹ In fact, increases of <5% in CA 19-9 were also associated with improved outcomes compared to patients with larger increases (OS, 10.3 months vs. 5.1 months; $P = .002$).

It is important to note that CA 19-9 may be undetectable in Lewis antigen-negative individuals.¹⁸² Furthermore, CA 19-9 may be falsely positive in cases of biliary infection (cholangitis), inflammation, or biliary obstruction (regardless of etiology) and do not necessarily indicate cancer or advanced disease.^{183,184} Preoperative measurement of CA 19-9 levels (category 3) is therefore best performed after biliary decompression is complete and bilirubin is normal. If biliary decompression is not performed in a jaundiced patient, CA 19-9 levels can be assessed (category 3), but they do not represent an accurate baseline.

The panel recommends measurement of serum CA 19-9 levels prior to surgery (category 3), following surgery immediately prior to administration of adjuvant therapy, and for surveillance (category 2B). The panel emphasizes the importance of obtaining a CA 19-9 measurement immediately before the therapeutic intervention to have an accurate baseline from which to follow response. Of note, a number of different methods are commercially available for quantifying this tumor-associated antigen. Measurements of serum levels of CA 19-9 using one testing method cannot be extrapolated to results obtained using a different procedure.

hENT1

A recent development in the field of advanced pancreatic cancer involves a potential predictive marker. Gemcitabine is a prodrug that must be taken into cells via a nucleoside transporter.¹⁸⁵ Human equilibrative nucleoside transporter 1 (hENT1) is a nucleoside transporter that has been studied as a predictor for response to gemcitabine. Preliminary clinical data have shown that hENT1 expression may in fact predict response to gemcitabine.¹⁸⁶⁻¹⁹¹

hENT1 has been validated in 2 retrospective analyses as a predictive biomarker for benefit from gemcitabine. A recent retrospective analysis of core tissue from patients treated on the adjuvant gemcitabine ESPAC-3 trial found that hENT1 expression was predictive of response to gemcitabine but not to 5-FU.¹⁸⁷ Median survival for patients treated with gemcitabine was 17.1 months versus 26.2 months for those with low versus high hENT1 expression, respectively ($P = .002$). In the 5-FU group, median survival was 25.6 months versus 21.9 months for the low and high hENT1 groups, respectively ($P = .36$). A similar analysis was performed on samples of patients treated on RTOG 9704.¹⁸⁶ As with the ESPAC-3 study, hENT1 expression was associated with OS (HR, 0.40;

95% CI, 0.22–0.75; $P = .03$) and DFS (HR, 0.39; 95% CI, 0.21–0.73; $P = .003$) in patients receiving gemcitabine, but hENT1 expression was not associated with OS (HR, 0.78; 95% CI, 0.47–1.27; $P = .31$) and DFS (HR, 0.72; 95% CI, 0.45–1.16; $P = .18$) in the group given 5-FU.

Thus, hENT1 appears to be an excellent predictive biomarker in the adjuvant setting based on the assay used in both of these studies (IHC with the 10D7G2 antibody). Other separate retrospective analyses of results from the adjuvant CONKO-001 trial and the AIO-PK0104 trial were unable to confirm these results using a different antibody for the IHC analysis (SP120).^{192,193}

Unfortunately, hENT1 could also not be validated in the metastatic setting in the LEAP trial, which also used the SP120 different assay to determine hENT1 expression. Results from the phase II, randomized, open-label LEAP trial, which compared a lipid-conjugated form of gemcitabine that does not require hENT1 for cell entry (CO-1.01) with gemcitabine in patients with metastatic disease with high versus low expression of hENT1, found that hENT1 expression was not predictive for outcomes in patients treated with gemcitabine.¹⁹⁴ Trial results also found no differences in OS between the 2 treatments in patients with low hENT2 expression (HR, 0.99; 95% CI, 0.75–1.33).

Further studies based on hENT1 expression using the 10D7G2 assay are handicapped by the fact that no commercial source of the antibody and no CLIA-approved testing are available.

Systemic Therapy Approaches

Systemic therapy is used in all settings of pancreatic adenocarcinoma. It is important that biopsy confirmation of pancreatic adenocarcinoma be obtained before treatment in all cases (see Table 2, below). At least 2 or 3 negative or indeterminate biopsies should be obtained before

entertaining alternative diagnoses (see *Differential Diagnoses*, above). A second opinion should also be obtained in such a case. Occasionally, other cancer types are confirmed, and the patient should be treated according to the appropriate NCCN Guideline. The data supporting the regimens used in pancreatic cancer are described below.

Gemcitabine Monotherapy

For patients with locally advanced or metastatic disease, gemcitabine has been established as providing clinical benefit and a modest survival advantage over treatment with bolus 5-FU.¹⁹⁵ The panel recommends gemcitabine monotherapy as one option for front-line therapy for patients with metastatic disease (category 1) or locally advanced disease and a good performance status. Because the approved indications for gemcitabine include the relief of symptoms, the panel also recommends gemcitabine monotherapy as a reasonable option for symptomatic patients with metastatic or locally advanced unresectable disease with poor performance status (category 1).

Gemcitabine monotherapy also has category-1 evidence supporting its use in the adjuvant setting. In the large phase III CONKO-001 trial, in which 368 patients without prior chemotherapy or RT were randomly assigned to adjuvant gemcitabine versus observation following macroscopically complete resection, an intention-to-treat (ITT) analysis of the data showed that the primary endpoint of increased DFS was met (13.4 months vs. 6.9 months; $P < .001$, log rank).¹⁹⁶ Final results from this study showed median OS to be improved significantly for patients in the gemcitabine arm (22.8 months vs. 20.2 months; HR, 0.76; 95% CI, 0.61–0.95; $P = .01$).¹⁹⁷ An absolute survival difference of 10.3% was observed between the two groups at 5 years (20.7% vs. 10.4%).¹⁹⁷

Fixed-Dose-Rate Gemcitabine

Studies have suggested that the infusion rate of gemcitabine may be important for its efficacy. Gemcitabine is a prodrug, which must be phosphorylated for antitumor activity. Clinical studies have shown that administering gemcitabine at a fixed dose rate (FDR) maximizes intracellular concentrations of the phosphorylated forms of gemcitabine.¹⁹⁸ In a randomized phase II trial of patients with locally advanced or metastatic pancreatic cancer, the infusion of gemcitabine at an FDR led to better survival compared with gemcitabine delivered at a higher dose, over 30 minutes.¹⁹⁹ In the phase III randomized ECOG-6201 trial of patients with advanced pancreatic cancer, median survival was increased in the group receiving FDR gemcitabine vs. standard gemcitabine (6.2 months vs. 4.9 months; $P = .04$), although this outcome did not satisfy the protocol-specified criteria for superiority.²⁰⁰ When gemcitabine is considered for the treatment of advanced pancreatic cancer, the NCCN Panel views FDR gemcitabine (10 mg/m²/min) as a reasonable alternative to the standard infusion of gemcitabine over 30 minutes (category 2B).

FDR gemcitabine is incorporated into some commonly used gemcitabine-based regimens (eg, GEMOX [gemcitabine, oxaliplatin]; GTX [gemcitabine, docetaxel, and capecitabine]). See *Gemcitabine Combinations*, below.^{201,202} The combination of FDR gemcitabine and capecitabine has also been found to be active and well-tolerated.²⁰³

Gemcitabine Combinations

The NCCN Panel acknowledges that, historically, combination chemotherapy did not appear to be superior to monotherapy in the era of 5-FU-based therapy. However, because gemcitabine is superior to bolus 5-FU in the advanced setting when efficacy endpoints of survival and relief from symptoms are used, it is now often combined with other

chemotherapeutic agents for patients with good performance status. Gemcitabine has been investigated in combination with potentially synergistic agents (such as cisplatin, oxaliplatin, capecitabine, 5-FU, and irinotecan) or in a multidrug combination (eg, cisplatin, epirubicin, gemcitabine, 5-FU).^{200-202,204-214} Two recent meta-analyses of randomized controlled trials found that gemcitabine combinations give a marginal benefit in OS over gemcitabine monotherapy in the advanced setting, with a significant increase in toxicity.^{215,216}

Combinations recommended in the advanced setting are discussed below. The panel does not consider the combination of gemcitabine plus docetaxel²¹⁷ or gemcitabine plus irinotecan^{214,217,218} to meet the criteria for inclusion in the guidelines. In addition, gemcitabine plus sorafenib is not recommended. The recent multi-center, double-blind, placebo-controlled, randomized phase III BAYPAN trial compared gemcitabine plus either sorafenib or placebo in chemotherapy-naïve patients with advanced or metastatic disease.²¹⁹ This trial did not meet its primary endpoint of progression-free survival (PFS) in its 104 patients (5.7 months vs. 3.8 months; $P = .90$). Gemcitabine combinations are currently being studied in the adjuvant setting.

Of note, results from several studies have indicated that the benefit of gemcitabine combination chemotherapy is predominantly seen in patients with good performance status.^{208,209,211}

Gemcitabine Plus Albumin-Bound Paclitaxel

Albumin-bound paclitaxel is a nanoparticle form of paclitaxel. In a publication of a phase I/II trial, 67 patients with advanced pancreatic cancer received gemcitabine plus albumin-bound paclitaxel. At the maximum tolerated dose, the partial response rate was 48%, with an additional 20% of patients demonstrating stable disease for ≥ 16 weeks. The median OS at this dose was 12.2 months.²²⁰

Based on these results, the large, open-label, international, randomized phase III MPACT trial was initiated in 861 patients with metastatic pancreatic cancer and no prior chemotherapy.²²¹ Participants were randomized to receive gemcitabine plus albumin-bound paclitaxel or gemcitabine alone. The trial met its primary endpoint of OS (8.7 months vs. 6.6 months; $P < .0001$; HR, 0.72).^{221,222} The addition of albumin-bound paclitaxel also improved other endpoints, including 1-year survival, 2-year survival, response rate, and PFS. The most common grade 3 or higher adverse events attributable to albumin-bound paclitaxel were neutropenia, fatigue, and neuropathy. Updated results of the MPACT trial show that long-term survival is possible with gemcitabine plus albumin-bound paclitaxel, as 3% of patients from that arm were alive at 42 months, whereas no patients were alive from the control arm at that time.²²²

For the 2013 guidelines, the panel upgraded the combination of gemcitabine plus albumin-bound paclitaxel from a category 2B to a category 1 recommendation for the treatment of patients with metastatic disease and good performance status based on these results. It is listed as a preferred option in this setting. By extrapolation of the data, the panel recommends this combination in the locally advanced, good performance status setting as well (category 2A). The panel also notes that this combination is an acceptable option in the neoadjuvant/borderline resectable setting.

Gemcitabine Plus Erlotinib and Other Targeted Therapeutics

Although phase II trial results of gemcitabine combined with new targeted drugs (eg, bevacizumab, cetuximab) were encouraging,^{223,224} results of phase III studies of combinations of gemcitabine with a biologic agent have indicated that only the combination of gemcitabine plus erlotinib is associated with a statistically significant increase in survival when compared to gemcitabine alone.²²⁵⁻²²⁹ Results of the

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Pancreatic Adenocarcinoma

CALGB phase III trial, which evaluated gemcitabine and bevacizumab (an anti-vascular endothelial growth factor [VEGF] antibody) compared with gemcitabine plus placebo in patients with locally advanced or metastatic pancreatic cancer, and the Southwest Oncology Group (SWOG) phase III randomized trial, which assessed cetuximab (which targets the epidermal growth factor receptor [EGFR]) plus gemcitabine versus gemcitabine alone, did not reveal improvements in survival upon addition of the biologic agent.^{226,227} In a phase III trial comparing gemcitabine and erlotinib with or without bevacizumab in patients with metastatic pancreatic cancer, bevacizumab did not improve OS, although a significant improvement in PFS was observed with the addition of bevacizumab to the gemcitabine/erlotinib combination.²²⁹ A randomized phase III trial of another VEGF inhibitor, axitinib, in combination with gemcitabine also failed to show any improvement in OS of patients with advanced pancreatic adenocarcinoma.²²⁸ Similarly, the VEGF trap ziv-aflibercept in combination with gemcitabine did not extend OS in a phase III trial in the metastatic setting.²³⁰

In contrast, in the phase III, double-blind, placebo-controlled NCIC CTG PA.3 trial of 569 patients with advanced or metastatic pancreatic cancer randomly assigned to receive erlotinib (which is an inhibitor of EGFR tyrosine kinase) plus gemcitabine versus gemcitabine alone, patients in the erlotinib arm showed statistically significant improvements in OS (HR, 0.82; $P = .038$) and PFS (HR, 0.77; $P = .004$) when compared to patients receiving gemcitabine alone.²²⁵ Median survival was 6.24 months and 1-year survival was 23%, compared with 5.91 months and 17% in the control arm. Adverse events, such as rash and diarrhea, were increased in the group receiving erlotinib, but most were grade 1 or 2.²²⁵ This trial, other trials, and community experience show that occurrence of grade 2 or higher skin rash is associated with better response and OS of patients receiving erlotinib.^{225,231,232}

The NCCN Panel recommends gemcitabine-erlotinib combination therapy as another option for patients with locally advanced or metastatic disease and good performance status (category 1). However, the panel notes that although this combination significantly improved survival, the actual benefit was small, suggesting that only a small subset of patients benefit.

Gemcitabine Plus Cisplatin

Data regarding the survival impact of combining gemcitabine with a platinum agent are conflicting, and results of randomized controlled trials have not provided support for use of gemcitabine plus cisplatin in the treatment of patients with advanced pancreatic cancer. Three phase III trials evaluating the combination of gemcitabine with cisplatin versus gemcitabine alone in patients with advanced pancreatic cancer failed to show a significant survival benefit for the combination over the single agent.^{205,206,209}

Nevertheless, selected patients may benefit from this regimen because patients with breast and ovarian cancers who are carriers of a *BRCA* mutation²³³⁻²³⁵ and selected patients with inherited forms of pancreatic cancer⁸¹ may have disease that is particularly sensitive to a platinum agent. A retrospective study from Johns Hopkins University School of Medicine of patients with metastatic pancreatic cancer and a family history of breast, ovarian, or pancreatic cancers suggested that response to gemcitabine and cisplatin was superior even with one affected relative.²³⁶ Patients with a family history of pancreatic cancer alone demonstrated a large survival advantage when treated with platinum-based chemotherapy (6.3 vs. 22.9 months; HR, 0.34; 95% CI, 0.15–0.74; $P < .01$).²³⁶ Furthermore, in a recent report, 5 of 6 patients with known *BRCA* mutations and metastatic pancreatic adenocarcinoma treated with a platinum-based regimen at Memorial Sloan Kettering Cancer Center showed a radiographic partial

response.²³⁷ Thus, gemcitabine plus cisplatin may be a good choice in selected patients with disease characterized by hereditary risk factors (eg, *BRCA* or *PALB2* mutations). The panel recommends gemcitabine plus cisplatin for patients with metastatic disease, especially those with possible hereditary cancers, as a category 2A recommendation.

Gemcitabine Plus Fluoropyrimidine

A number of randomized trials have investigated the combination of gemcitabine with a fluoropyrimidine in patients with advanced pancreatic cancer. The ECOG E2297 trial compared gemcitabine monotherapy with gemcitabine and bolus 5-FU/leucovorin in patients with advanced pancreatic cancer; no statistically significant survival advantage was observed for patients receiving the combination regimen.²⁰⁴ A randomized study in 533 patients with advanced disease found that PFS and objective response rates were significantly improved in patients receiving gemcitabine plus capecitabine when compared with gemcitabine alone, although a trend toward an improvement in OS for the combination arm did not reach statistical significance.²⁰⁷ Similarly, results from another smaller phase III trial evaluating this combination did not demonstrate an OS advantage for overall study population receiving the combination of gemcitabine with capecitabine, although a post-hoc analysis showed OS to be significantly increased in the subgroup of patients with good performance status.²¹¹ A recent meta-analysis of 8 randomized controlled trials, including >2000 patients, found that OS was significantly improved when a fluoropyrimidine was added to gemcitabine.²³⁸ In particular, OS was better in patients receiving gemcitabine plus capecitabine than in patients receiving gemcitabine alone (HR, 0.87; *P* = .03).

Although there are concerns about dosing and toxicity of capecitabine in a U.S population, results from a recent study suggest that a biweekly

regimen of fixed-dose gemcitabine in combination with capecitabine is both effective and well tolerated in patients with advanced disease.²⁰³

The NCCN Panel considers gemcitabine-based combination therapy with capecitabine to be a reasonable option (category 2A) for patients with locally advanced or metastatic disease and a good performance status who are interested in pursuing more aggressive therapy outside a clinical trial.

GTx Regimen

The panel includes the combination of gemcitabine, docetaxel, and capecitabine (GTx regimen) as a category 2B recommendation for the treatment of patients with advanced disease and good performance status. In a report of 35 patients with metastatic pancreatic cancer treated with this regimen, the authors reported an overall response rate of 29% (all had partial responses), with an additional 31% of patients exhibiting a minor response or stable disease.²⁰² The median survival was 11.2 months for all patients and 13.5 months for patients exhibiting a partial response. This regimen demonstrated significant toxicities, however, with 14% of patients having grade 3/4 leukopenia, 14% having grade 3/4 thrombocytopenia, and 9% having grade 3/4 anemia. A recent retrospective case-review study at The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins found similar results, with a median OS of 11.6 months and grade 3 or greater hematologic and non-hematologic toxicity rates of 41% and 9%, respectively.²³⁹

5-FU/Leucovorin

5-FU with leucovorin is listed in the guidelines as a category 1 option in the adjuvant setting. Results from the European Study Group for Pancreatic Cancer (ESPAC)-1 trial, reported by Neoptolemos and colleagues, suggested that 5-FU/leucovorin is superior to observation.²⁴⁰ In addition, results from the ESPAC-3 trial of bolus 5-

FU/leucovorin versus gemcitabine following surgery showed no difference in median OS between the arms (23.0 months and 23.6 months, respectively).²⁴¹

Leucovorin Shortage

There is currently a shortage of leucovorin in the United States. There are no specific data to guide management under these circumstances, and all proposed strategies are empiric. The panel recommends several possible options to help alleviate the problems associated with this shortage. One is the use of levo-leucovorin, which is commonly used in Europe. A dose of 200 mg/m² of levo-leucovorin is equivalent to 400 mg/m² of standard leucovorin. Another option is for practices or institutions to use lower doses of leucovorin for all doses in all patients, since the panel feels that lower doses are likely to be as efficacious as higher doses, based on several studies. The QUASAR study found that 175 mg leucovorin gave similar survival and 3-year recurrence rates as 25 mg leucovorin when given with bolus 5-FU to patients as adjuvant therapy following R0 resections for colorectal cancer.²⁴² Another study showed no difference in response rate or survival in patients with metastatic colorectal cancer receiving bolus 5-FU with either high-dose (500 mg/m²) or low-dose (20 mg/m²) leucovorin.²⁴³ Also, the Mayo Clinic and North Central Cancer Treatment Group (NCTTG) determined that there was no therapeutic difference between the use of high- (200 mg/m²) or low- (20 mg/m²) dose leucovorin with bolus 5-FU in the treatment of advanced colorectal cancer, although 5-FU doses were different in the 2 arms.²⁴⁴ Finally, if none of the above options are available, treatment without leucovorin would be reasonable. For patients who tolerate this without grade II or higher toxicity, a modest increase in 5-FU dose (in the range of 10%) may be considered.

FOLFIRINOX

In 2003, a French group reported the results of an open phase I study to assess the feasibility of a combination therapy consisting of 5-FU/leucovorin plus oxaliplatin and irinotecan (FOLFIRINOX) for the treatment of patients with metastatic solid tumors.²⁴⁵ Their study included 2 patients with pancreatic cancer, and the regimen showed anti-tumor activity. A subsequent multicenter phase II trial specifically for patients with advanced pancreatic adenocarcinoma demonstrated promising response rates.²⁴⁶ A later randomized phase II trial showed a response rate of >30% to FOLFIRINOX in patients with metastatic pancreatic cancer.²⁴⁷

Results from the randomized phase III PRODIGE trial evaluating FOLFIRINOX versus gemcitabine in patients with metastatic pancreatic cancer and good performance status showed dramatic improvements in both median PFS (6.4 months vs. 3.3 months; $P < .001$) and median OS (11.1 months vs. 6.8 months; $P < .001$), in favor of the group receiving FOLFIRINOX.²⁴⁸ Because of these strong results, the panel added FOLFIRINOX as a preferred, category 1 recommendation for first-line treatment of good performance status patients with metastatic pancreatic cancer in 2011. It is listed as a category 2A recommendation for patients with locally advanced unresectable disease by extrapolation. The panel also lists this regimen as an acceptable option in the neoadjuvant/borderline resectable setting.

There are, however, some concerns about the toxicity of the FOLFIRINOX regimen. In the PRODIGE trial, some of the grade 3/4 toxicity rates that were significantly greater in the FOLFIRINOX group than in the gemcitabine group were 45.7% for neutropenia, 12.7% for diarrhea, 9.1% for thrombocytopenia, and 9.0% for sensory neuropathy.²⁴⁸ Despite the high levels of toxicity, no toxic deaths have

been reported.²⁴⁶⁻²⁴⁸ Furthermore, the PRODIGE trial determined that, despite this toxicity, fewer patients in the FOLFIRINOX group than in the gemcitabine group experienced a degradation in their quality of life at 6 months (31% vs. 66%, $P < .01$).²⁴⁸ A more detailed analysis of the quality of life of patients in this trial has been published and shows that FOLFIRINOX maintained and even improved quality of life more than gemcitabine did.²⁴⁹

The panel appreciates that toxicity of FOLFIRINOX can be managed with a variety of approaches. For example, a group from Memorial Sloan Kettering Cancer Center reported good activity and acceptable toxicity of first-line FOLFIRINOX at 80% dose intensity with routine growth factor support in carefully selected patients with metastatic or locally advanced disease.²⁵⁰ Median OS was 12.5 months in the metastatic setting and 13.7 months in patients with locally advanced disease.

Capecitabine and Continuous Infusion 5-FU

The panel lists capecitabine monotherapy and continuous infusion 5-FU as first-line treatment options for patients with locally advanced unresectable or metastatic disease (category 2B). They are also recommended as options in the adjuvant settings (category 2A for continuous infusion 5-FU and category 2B for capecitabine). The capecitabine recommendation is supported by a randomized phase III trial from the Arbeitsgemeinschaft Internistische Onkologie (AIO) group in which OS was similar in patients with advanced pancreatic cancer receiving capecitabine plus erlotinib followed by gemcitabine monotherapy or gemcitabine plus erlotinib followed by capecitabine monotherapy.²⁵¹

Note that the capecitabine dose recommended by the panel (1000 mg/m² PO twice daily) is less than the dose described by Cartwright

and colleagues, because the higher dose has been associated with increased toxicity (eg, diarrhea, hand and foot syndrome).²⁵²

Fluoropyrimidine Plus Oxaliplatin

The combination of a fluoropyrimidine (5-FU/leucovorin or capecitabine) with oxaliplatin is listed as a possible first-line treatment for metastatic or locally advanced disease (category 2B). The panel bases these recommendations on the randomized phase III CONKO-003 trial (5-FU/leucovorin/oxaliplatin vs. best supportive care) and on a phase II study (CapeOx).^{253,254} Both of these studies only enrolled patients who had received 1 prior chemotherapy regimen, but the panel feels the extrapolation to first-line therapy is appropriate (category 2B).

Possible Role of Maintenance Therapy in Advanced Disease

With the success of more effective regimens in patients with advanced disease, questions have been raised about how best to manage the treatment-free interval prior to disease progression. Options include stopping treatment, dropping the most toxic agents, and using different agents for maintenance therapy.

A recent randomized phase II trial (PACT-12) had intriguing results that suggest maintenance therapy with the angiogenesis inhibitor sunitinib after a full course of first-line treatment may have a benefit in some patients with metastatic disease.²⁵⁵ Patients without evidence of progression after 6 months of initial therapy (n=55; mostly gemcitabine combinations) were randomized to sunitinib or observation. Median OS was 9.2 months in the observation group versus 10.6 months in the sunitinib group (HR, 0.71; 95% CI, 0.40–1.26; $P = .11$). The small sample size precludes strong conclusions; however, the 1- and 2-year survival rates were 36% and 7% in the observation arm compared with 41% and 23% in the sunitinib arm, suggesting that a subset of patients derive significant benefit. Anti-angiogenic agents have not been

successful in the treatment of pancreatic cancer to date. However, results of the PACT-12 trial suggest that there may in fact be a role for these compounds in this disease. Angiogenesis inhibitors may be more useful after more effective first-line treatments. Clearly additional trials in this important area are needed.

Second-Line Systemic Therapy in the Advanced Setting

A recent systematic review of clinical trials that assessed the efficacy of second-line therapy after gemcitabine in pancreatic cancer concluded that, while data are very limited, evidence suggests an advantage of additional chemotherapy over best supportive care.²⁵⁶ For patients with advanced disease who have received prior gemcitabine-based therapy, fluoropyrimidine-based chemotherapy regimens are acceptable second-line options.^{253,254,257} Gemcitabine-based therapy can be given to those previously treated with fluoropyrimidine-based therapy.

Results from the phase III CONKO-003 trial presented in 2008 showed significant improvements in both median PFS (13 weeks vs. 9 weeks; $P = .012$) and median OS (20 weeks vs. 13 weeks; $P = .014$) when oxaliplatin was added to 5-FU/leucovorin,^{258,259} making this regimen the standard approach for second-line therapy for patients without prior exposure to fluoropyrimidine-based therapy at that time. Final results of the trial were published in 2014.²⁶⁰ The median OS in the OFF arm was 5.9 months (95% CI, 4.1–7.4), whereas it was 3.3 months (95% CI, 2.7–4.0) in the 5-FU/LV arm, for a significant improvement in the hazard ratio (HR, 0.66; 95% CI, 0.48–0.91; $P = .01$).

However, results from the open-label phase III PANCREOX trial show that the addition of oxaliplatin to 5-FU/LV in second-line treatment may be detrimental.²⁶¹ In this trial, 108 patients with advanced pancreatic cancer who progressed on gemcitabine-based treatment were randomized to receive second-line mFOLFOX6 or infusional 5FU/LV.

No difference was seen in median PFS (3.1 vs 2.9 months; $P = .99$), but median OS was worse in those in the FOLFOX arm (6.1 vs. 9.9 months; $P = .02$). Furthermore, the addition of oxaliplatin resulted in increased toxicity, with rates of grade 3/4 adverse events of 63% in the FOLFOX arm and of 11% in the 5-FU/LV arm.

The AIO-PK0104 trial also assessed second-line therapy in a randomized crossover trial and found capecitabine to be efficacious after progression on gemcitabine/erlotinib in patients with advanced disease.²⁶² In this trial, capecitabine/erlotinib followed by gemcitabine gave similar outcomes to the aforementioned sequence.

Chemoradiation Approaches

In patients with pancreatic cancer, radiation is usually given concurrently with gemcitabine- or fluoropyrimidine-based chemotherapy. Chemotherapy is used as a radiosensitizer, increasing the toxicity of radiation to tumor cells. Although the mechanism of radiosensitization is not entirely clear, it is postulated that gemcitabine and fluoropyrimidines decrease the number of tumor cells in the S phase of the cell cycle, a stage at which cells are resistant to radiation damage.²⁶³

Chemoradiation is sometimes used for pancreatic cancer in the adjuvant setting, because of its potential to decrease the likelihood of local recurrence. It is also sometimes used in the locally advanced setting, namely in those patients who do not progress during initial chemotherapy. Chemoradiation is also often incorporated into neoadjuvant regimens, although randomized trials demonstrating the role of chemoradiation in this setting have not been done.

Chemoradiation can also be given as second-line therapy in patients with locally advanced unresectable disease or in resected patients if it was not previously given and if the primary site is the sole site of

progression. Finally radiation, without chemotherapy, is used in the metastatic setting as palliation for pain refractory to narcotic therapy. Varying levels of evidence support the use of chemoradiation in each setting, as discussed in more detail below.

Adjuvant Chemoradiation

In 1985, the Gastrointestinal Tumor Study Group (GITSG) initially reported that the median survival of patients undergoing pancreatoduodenectomy could be prolonged almost 2-fold by postoperative chemoradiation.^{264,265} In this study, patients were randomly assigned to either observation or RT combined with an intermittent bolus of 5-FU after resection. A standard split course of 4,000 cGy was used. 5-FU, 500 mg/m² daily for 3 days, was given concurrently with each 2,000-cGy segment of RT. The 5-FU regimen was then continued weekly for a full 2 years. In addition to a prolonged median survival, chemoradiation also resulted in a 2-year actuarial survival of 42%, compared with 15% in the control group.²⁶⁴

Other studies have also shown an advantage to adjuvant chemoradiation over observation after resection. EORTC conducted a phase III trial (40891) in patients with both ampullary and pancreatic adenocarcinoma assessing adjuvant radiotherapy and 5-FU versus observation alone after surgery. They found that the benefit of therapy was small in a subset of patients with pancreatic adenocarcinoma and was not statistically significant.²⁶⁶ At a median follow-up of 11.7 years, no statistically significant differences were observed in the different study arms with respect to PFS or OS for the subset of patients with pancreatic cancer.²⁶⁷

More contemporary studies have compared different regimens incorporating chemoradiation. The Radiation Therapy Oncology Group study RTOG 9704 was a phase III study that evaluated postoperative

adjuvant treatment of resected pancreatic adenocarcinoma using either gemcitabine or fluorouracil for 3 weeks before and 12 weeks after 5-FU-based chemoradiation for both groups.²⁶⁸ This trial, which utilized daily fractionated radiotherapy, included prospective quality assurance of all patients, including central review of preoperative CT imaging and radiation fields.²⁶⁹ Results of this study showed that, for patients with tumors of the pancreas head (representing 388 of the 451 patients enrolled in the trial), there was a non-statistically significant increase in OS in the gemcitabine arm compared with the 5-FU arm (median and 3-year survival of 20.5 months and 31% vs. 16.9 months and 22%; $P = .09$); this benefit became more pronounced on multivariate analysis (HR, 0.80; 95% CI, 0.63–1.00; $P = .05$). The recently published 5-year analysis of RTOG 9704 showed that there was in fact no difference in OS between the two groups, although patients with tumors in the head of the pancreas showed a trend toward improved OS with gemcitabine ($P = .08$) upon multivariate analysis.²⁷⁰

The Role of Radiation in Adjuvant Regimens

The majority of the data comparing chemotherapy to chemoradiation in the adjuvant setting do not generally show an advantage to the addition of radiation. Results of ESPAC-1 suggested that the addition of radiation to adjuvant 5-FU chemotherapy may be unnecessary and perhaps even harmful (OS, 13.9, 21.6, and 19.9 months for chemoradiation, chemotherapy, and chemotherapy plus chemoradiation, respectively),²⁴⁰ although the ESPAC-1 trial has been criticized for lack of attention to quality control for RT.²⁷¹⁻²⁷³ A phase II study by GERCOR randomized patients to adjuvant gemcitabine or adjuvant gemcitabine-based chemoradiation.²⁷⁴ No differences were seen in OS (24.4 months vs. 24.3 months) or DFS (10.9 months vs. 11.8 months) between the groups, but with only 45 patients in each arm no P values were reported. In addition, the multicenter, open-label,

randomized phase III CapRI trial recently found that adjuvant chemoradiation with 5-FU, cisplatin, and interferon alfa-2b (IFN α -2b) followed by 5-FU chemotherapy gave outcomes no better than adjuvant treatment with 5-FU alone.²⁷⁵

A 2012 meta-analysis of 15 prospective, randomized trials found that adjuvant chemoradiation did not improve DFS, 2-year survival, or OS (odds ratio, 0.99; $P = .93$) compared to surgery alone, while adjuvant chemotherapy improved all 3 outcomes (odds ratio for OS, 1.98; $P < .001$).²⁷⁶ A 2013 meta-analysis of 9 trials found similar results, with HRs for death compared to no adjuvant treatment of 0.62 for 5-FU (95% CI, 0.42–0.88), 0.68 for gemcitabine (95% CI, 0.44–1.07), 0.91 for chemoradiation (95% CI, 0.55–1.46), 0.54 for chemoradiation plus 5-FU (95% CI, 0.15–1.80), and 0.44 for chemoradiation plus gemcitabine (95% CI, 0.10–1.81).²⁷⁷

However, a population-based assessment of outcomes of patients in the NCDB with pancreatic cancer resected from 1998 to 2002 found the opposite result: chemoradiation gave better OS than chemotherapy in a performance-status–matched comparison to no adjuvant treatment (HR, 0.70; 95% CI, 0.61–0.80 vs HR, 1.04; 95% CI, 0.93–1.18).²⁷⁸ A multi-institutional pooled analysis of 955 consecutive patients who had R0-1 resections for pancreatic cancer also supports the supposition that adjuvant chemoradiation improved survival compared to chemotherapy alone (OS, 39.9 months vs. 27.8 months; $P < .001$).²⁷⁹

To definitively clarify the role of chemoradiation following gemcitabine monotherapy in the adjuvant setting, RTOG is conducting trial 0848 (ClinicalTrials.gov NCT01013649). Patients without evidence of progressive disease after 5 cycles of gemcitabine-based chemotherapy are being randomized to 1 additional round of chemotherapy or 1 additional round of chemotherapy followed by chemoradiation with

capecitabine or 5-FU. The primary endpoint is OS, and the trial is estimated to be completed in 2020.

Benefit of Adjuvant Chemoradiation in Patient Subsets

It has been suggested that subsets of patients (eg, patients with R1 resections or positive lymph nodes) may be more likely to benefit from adjuvant chemoradiation.

Studies that have looked at R0 or R1 subsets of patients have found mixed results. For instance, patients treated in the ESPAC-1 trial did not derive a benefit from the addition of radiation to adjuvant chemotherapy, irrespective of margin status.²⁸⁰ In contrast, results from a prospectively collected database of 616 patients with resected pancreatic cancer at the Johns Hopkins Hospital found that adjuvant chemoradiation benefited both the R0 and R1 subsets compared to observation alone.²⁸¹ The Mayo Clinic performed a retrospective review of 466 patients who had R0 resections for pancreatic adenocarcinoma, and found an OS benefit of adjuvant chemoradiation over observation.²⁸² In addition, a retrospective review of resected >1200 patients from the Johns Hopkins Hospital and the Mayo Clinic who received adjuvant 5-FU-based chemoradiation or were observed following resection found that chemoradiation improved outcomes regardless of margin status (R0: RR, 0.61; 95% CI, 0.47–0.77, $P < .001$. R1: RR, 0.52; 95% CI, 0.36–0.74; $P < .001$).²⁸³ A meta-analysis of 4 randomized controlled trials found evidence for an increased survival benefit of adjuvant chemoradiation in the R1 subset (HR for death, 0.72; 95% CI, 0.47–1.10) over the R0 subset (HR for death, 1.19; 95% CI, 0.95–1.49).²⁸⁴ Fewer analyses have looked at the role of chemoradiation in resected patients with positive lymph nodes. One retrospective review compared outcomes of 94 patients who underwent distal pancreatectomy at the Johns Hopkins Hospital and either received adjuvant chemoradiation or were just observed following resection.²⁸⁵ An exploratory subset

analysis suggested that patients with positive lymph nodes derived greater benefit from adjuvant chemoradiation than those with negative nodes. In addition, a meta-analysis of 4 randomized controlled adjuvant trials found that chemoradiation had a similar lack of benefit in lymph node-positive and -negative patients.²⁸⁶

Chemoradiation for Locally Advanced Disease

Chemoradiation is a conventional option for the management of unresectable locoregional pancreatic cancer, although the utility of chemoradiation in this population of patients is controversial.²⁸⁷ It is mainly used in selected patients who do not develop metastatic disease during initial chemotherapy.

The role of chemoradiation in locoregional pancreatic cancer was initially defined in a trial conducted in locally advanced disease by GITSG.²⁶⁵ In this study, the combination of bolus 5-FU and split-course radiation (total dose, 4000 cGy) was compared with radiation alone or with 6000 cGy combined with 5-FU. A nearly 2-fold increase in median survival (42.2 vs. 22.9 weeks) was observed with the regimen of bolus 5-FU and 4000 cGy compared with radiation alone. Subsequent generations of studies have sought to optimize the use of 5-FU, and most contemporary studies no longer use split-course radiation.²⁸⁸ Gemcitabine has also been used as a radiation sensitizer in the locally advanced setting.²⁸⁹⁻²⁹³ Evidence suggests that concurrent gemcitabine and radiation can yield similar or better outcomes when compared with 5-FU-based chemoradiation in the setting of locally advanced disease.^{288,292,294,295} The use of capecitabine as a radiosensitizer has also been assessed in this setting and appears to be effective.²⁹⁶

A recent meta-analysis identified 15 randomized controlled trials (1128 patients) that compared chemoradiation to either chemotherapy or radiation in the locally advanced setting.²⁹⁷ Whereas combined modality

therapy significantly improved survival compared to radiation alone, survival was the same when compared to those receiving chemotherapy alone. Increased toxicity was observed in the chemoradiation group.

Upfront Chemoradiation in Locally Advanced Disease

Results of 2 early randomized trials comparing upfront chemoradiation to chemotherapy in locally advanced disease were contradictory.^{298,299} Three phase II trials also assessed the upfront chemoradiation approach in locally advanced pancreatic adenocarcinoma, with median survival rates ranging from 8.2 to 9 months.^{289,300-302} Results from small, single-arm trials of upfront chemotherapy followed by chemoradiation in locally advanced disease have been discussed.³⁰³

The more recent phase III randomized ECOG-4201 trial, which assessed gemcitabine compared with gemcitabine plus RT followed by gemcitabine alone in patients with locally advanced, unresectable pancreatic cancer, was closed early due to poor accrual. However, an ITT analysis of data for the 74 patients enrolled in this study showed that median OS was significantly longer in the chemoradiation therapy arm of the study (11.1 months vs. 9.2 months; $P = .017$).³⁰⁴ However, the poor accrual rate decreased its statistical power, there was no difference in PFS, and the confidence intervals for OS overlapped between the two groups of patients, leading some to state that the results do not rise to the level of evidence required to determine standard of care.³⁰⁵

The benefit of chemotherapy versus chemoradiation was also addressed in the phase III FFCD-SFRO study from France, in which patients with locally advanced pancreatic cancer were randomly assigned to receive either gemcitabine alone or an intensive induction regimen of chemoradiation with 5-FU plus cisplatin followed by

gemcitabine maintenance treatment.³⁰⁶ In this study, gemcitabine alone was associated with a significantly increased OS rate at 1 year compared with chemoradiation (53% vs. 32%; HR, 0.54; 95% CI, 0.31–0.96; $P = .006$). This study was stopped before the planned accrual, because an interim analysis revealed that patients in the chemoradiation arm had a lower survival rate. Also, patients in the chemoradiation arm experienced severe toxicity and were more likely to receive a shorter course of maintenance therapy with gemcitabine, suggesting that the observed differences in survival were most likely attributable to the extreme toxicity of this particular chemoradiation regimen.

Thus, the role of upfront chemoradiation in the setting of locally advanced pancreatic cancer is still undefined. The panel points out that if patients present with poorly controlled pain or local invasion with bleeding, it may be preferable to start with upfront chemoradiation therapy.^{289,291}

Chemoradiation Following Chemotherapy in Locally Advanced Disease

Starting with 2 to 6 cycles of systemic chemotherapy followed by chemoradiation therapy is an option for selected patients with unresectable disease and good performance status who have not developed metastatic disease.³⁰⁷⁻³⁰⁹ This sequence is especially recommended in cases where: 1) it is highly unlikely that the patient will become resectable (ie, complete encasement of superior mesenteric/celiac arteries); 2) there are suspicious metastases; or 3) the patient may not be able to tolerate chemoradiation. Employing an initial course of chemotherapy may improve systemic disease control in these cases. In addition, the natural history of the disease can become apparent during the initial chemotherapy, thus allowing the selection of patients most likely to benefit from subsequent chemoradiation. For example, a retrospective analysis of outcomes from the GERCOR

studies indicated that first-line treatment with chemotherapy may be a useful strategy for selecting patients with locally advanced disease who are more likely to benefit from subsequent chemoradiation therapy.³⁰⁷

However, preliminary data from the international phase III LAP 07 trial showed no clear survival benefit (the primary outcome measure) with the addition of conventional chemoradiation following gemcitabine monotherapy.³¹⁰ In this study, 269 patients with disease control after induction gemcitabine-based chemotherapy were randomized to additional chemotherapy or to chemoradiation with capecitabine. Median OS was 16.5 months in the chemotherapy arm versus 15.3 months in the chemoradiation arm (HR, 1.03; 95% CI, 0.79–1.34; $P = .83$). Differences were noted in other potentially meaningful outcomes such as time to reinitiation of therapy (159 days in the chemoradiation arm vs. 96 days in the control arm; $P = .05$) and local tumor progression (34% in the chemoradiation arm vs. 65% in the control arm; $P < .0001$).³¹¹ Because there are now more active chemotherapy regimens than gemcitabine monotherapy, additional studies are planned to assess the role of radiation after more active chemotherapy.

Advanced Radiation Techniques

IMRT is increasingly being applied for therapy of locally advanced pancreatic adenocarcinoma and in the adjuvant setting with the aim of increasing radiation dose to the gross tumor while minimizing toxicity to surrounding tissues.³¹²⁻³¹⁶ A retrospective treatment planning study evaluated the dose escalation that might have been possible in 15 patients with locally advanced, unresectable pancreatic adenocarcinoma if IMRT had been used instead of 3-D conformal planning.³¹⁶ While the authors concluded that the IMRT plans would allow for significant increase in target volume dose with substantial dose reductions to local organs at risk, there is no clear consensus on the

appropriate maximum dose of radiation when IMRT is used. Results of a recent study demonstrated that IMRT resulted in reduced grade 3/4 toxicities when the authors made a cross-study comparison of toxicities in patients who received a similar 5-FU-based regimen with 3-D conformal radiation in the RTOG 9704 trial.^{268,317} Comparing the 2 trials, rates of grade 3/4 nausea and vomiting were 0% vs. 11% ($P = .024$), and rates of grade 3/4 diarrhea were 3% vs. 18% ($P = .017$),³¹⁷ suggesting that IMRT may be well tolerated and allow for higher radiation doses to the tumor.³¹⁷ There is no clear consensus on the appropriate maximum dose of radiation when IMRT technique is used.

Stereotactic body radiotherapy (SBRT) is another technique aimed at increasing dose to the gross tumor while sparing radiation to nearby healthy tissue.³¹⁸⁻³²³ Retrospective analysis of 77 patients with unresectable disease demonstrated that while SBRT gave effective local control, it gave no improvement to OS and was associated with significant toxicities.³¹⁸ However, another retrospective review of 71 patients reported a median OS of 10.3 months with only 3 patients (4%) experiencing grade 3 toxicity.³²¹ No standard total dose or dose per fraction has been established for SBRT, and the panel currently recommends that SBRT only be utilized as part of a clinical trial.

Intraoperative radiation therapy (IORT) can allow for higher doses of radiation because sensitive structures can be excluded from the radiation fields. IORT is sometimes administered to patients with borderline resectable disease who have received maximal neoadjuvant therapy to sterilize close or involved margins at the time of surgery, although data in this setting are lacking. It is also sometimes used when a patient is found to be unresectable at the time of surgery and in cases of locally recurrent disease. Most studies of IORT in patients with locally advanced pancreatic cancer found that while local control may be improved, no change in survival is evident with use of IORT because of

the high frequency at which metastatic disease develops.³²⁴⁻³²⁷ Some groups, however, believe that IORT can offer benefits in very carefully selected patients with non-metastatic disease.³²⁸⁻³³⁰ Overall, there is no clear established role for IORT in patients with pancreatic cancer,³³¹ and the panel believes it should only be performed at specialized centers.

Management of Metastatic Disease

The primary goals of treatment for metastatic pancreatic cancer are palliation and lengthened survival. Survival benefits are usually limited to patients with adequate performance status (ECOG 0-1, with good pain management, patent biliary stent, and adequate nutritional intake). Systemic therapy is therefore recommended for patients with metastatic disease and good performance status, as described in *Systemic Therapy Approaches*, above, and in the guidelines.

Patients who present with poor performance status may benefit from the administration of gemcitabine (category 1 recommendation), but comfort-directed measures are always paramount (see *Palliative and Supportive Care*, below, and the NCCN Guidelines for Supportive Care, available at www.NCCN.org). An alternative option for these patients is palliative and best supportive care.

Before initiating cytotoxic therapy, an open dialogue regarding the goals and side effects of treatment should take place and, if needed, adjunctive strategies can be used (see *Palliative and Supportive Care*, below). Of note, debilitated patients with advanced disease may have abrupt changes in clinical status. Therefore, if treatment is begun, it should proceed with close follow-up. Patients may experience sudden onset of bleeding or thromboembolism, rapidly escalating pain, biliary stent occlusion, cholangitis, or other infections. Moreover, clinically meaningful tumor progression may develop quickly, and tumor-related symptoms may be inappropriately attributed to chemotherapy or other

causes. For instance, patients who complain of intractable nausea and vomiting may have gastric outlet obstruction rather than chemotherapy-induced emesis. Peritoneal carcinomatosis may manifest as ascites or in its more subtle form, as abdominal bloating, as decreased oral intake, and as constipation.

For patients who do well on initial therapy, a chemotherapy holiday is appropriate, or maintenance therapy can be considered (see, *Possible Role of Maintenance Therapy*, above). After progression, second-line therapy is possible, especially in patients who maintain a good performance status (see *Second-Line Systemic Therapy in the Advanced Setting*, above).

Management of Locally Advanced Disease

As in the metastatic setting, the primary goals of treatment of patients with unresectable, locoregional pancreatic cancer are palliation and lengthened survival. Also, as in metastatic disease, patients with locally advanced disease are treated with systemic therapy based on their performance status. Gemcitabine (category 1) and palliative and best supportive care are options for patients with poor performance status, whereas patients with good performance status can be treated with more intensive therapy (eg, FOLFIRINOX [category 2A], gemcitabine/albumin-bound paclitaxel [category 2A]) or with gemcitabine monotherapy (category 2A), as described in *Systemic Therapy Approaches*, above, and in the guidelines.

Historically, most studies in the locally advanced setting used gemcitabine monotherapy. However, there is an increasing emphasis on understanding the role of modern, more active regimens in locoregional unresectable disease. The experience with FOLFIRINOX in 22 patients with locally advanced pancreatic cancer at the Massachusetts General Hospital Cancer Center through February 2012

was recently reported.³³² An overall response rate of 27% was observed, and the median PFS was 11.7 months. Five patients (23%) were able to undergo R0 resections, although 3 of these patients experienced distant recurrence by 5 months. It was also reported that 32% of patients receiving FOLFIRINOX required ≥ 1 hospitalization or visit to the emergency department during treatment.

Other studies and case reports addressing the use of chemotherapy with or without chemoradiation in patients with locally unresectable disease have noted that the opportunity for curative intent resection occasionally arises.³³²⁻³⁴¹ The panel believes that patients with a significant response to chemotherapy and/or chemoradiation may be considered for surgical resection, but acknowledges that such conversions are rare in patients with true locally advanced disease. Following resection, these patients have similar survival rates as those initially determined to be resectable.³⁴²

The use of chemoradiation following chemotherapy in locally advanced disease is discussed above (See *Chemoradiation for Locally Advanced Disease*).

Management of Resectable and Borderline Resectable Disease

Surgical Management

Surgical resection is the only potentially curative technique for managing pancreatic cancer. However, more than 80% of patients present with disease that cannot be cured with surgical resection.³⁴³ Early concerns about high mortality associated with various pancreatic resection procedures³⁴⁴ have now been lessened by studies demonstrating an acceptably low (<5%) mortality in experienced centers (see *Effect of Clinical Volume*, below).³⁴⁵ Even under the most optimal clinical trial conditions, however, the median survival of resected

patients following adjuvant therapy ranges from 20.1 to 23.6 months.^{196,240,241,268} Negative margin status (ie, R0 resection), tumor DNA content, tumor size, and absence of lymph node metastases are the strongest prognostic indicators for long-term patient survival.³⁴⁶⁻³⁴⁸ With respect to margin status, there is evidence for the converse statement—the survival benefits of an R1 resection may be comparable to definitive chemoradiation without surgery.³⁴⁹⁻³⁵¹

Criteria for Resection

The NCCN Panel recommends that decisions about diagnostic management and resectability always involve multidisciplinary consultation at high-volume centers with use of appropriate high-quality imaging studies to evaluate the extent of disease. Although it is clear that patients with visceral, peritoneal, or pleural metastases or with metastases to nodes beyond the field of resection derive no benefit from resection, institutions differ in their approaches to patients with locoregional disease involvement (pancreas and peripancreatic lymph nodes).

Based on their clinical experience with the primary management of pancreatic tumors, an expert consensus group developed criteria to define tumor resectability so as to improve patient selection for surgery and increase the likelihood of an R0 resection.^{108,352} Other groups have also put forth definitions of resectability of pancreatic cancer.³⁵³⁻³⁵⁵ A more restrictive definition of borderline resectable pancreatic tumors has also been described.³⁵⁶ This definition uses degrees of contact (eg, interface between tumor and SMA measuring <180° of vessel wall circumference) rather than subjective terms such as abutment and impingement. The panel endorses this definition for use in clinical trials. Using any of these sets of criteria, tumors are classified as resectable; borderline resectable; or unresectable (ie, locally advanced or metastatic disease).

The NCCN Pancreatic Adenocarcinoma panel has adapted the criteria put forth by other groups and lists its recommended criteria for defining resectability status in the guidelines. The consensus of the panel is that patients should be selected for surgery on the basis of curative intent as determined by the probability of obtaining negative (R0) resection margins. Overall, the likelihood of attaining negative margins is the key criterion for consideration when determining whether a patient is a potential candidate for resection.^{355,357} In this context, a borderline resectable lesion can be defined as one in which there is a higher likelihood of an incomplete resection. Patients at high risk for positive surgical margins are not considered to be good candidates for an upfront resection. Furthermore, the panel recommends that patient factors be considered when deciding whether a patient is a surgical candidate. Age of the patient, comorbidities, performance status, and frailty are all things to be discussed during the multidisciplinary review. Please refer to the NCCN Guidelines for Older Adult Oncology for further discussion of the treatment of older patients.

Primary Surgery for Pancreatic Cancer

The nature and extent of the surgery for resectable tumors depend on the location and size of the tumor. Because tumors of the body and tail cause symptoms late in their development, they are usually advanced at diagnosis and are rarely resectable. When tumors in the pancreatic tail are resectable, distal pancreatectomy, in which the surgeon removes the tail and body of the pancreas, as well as the spleen, is commonly performed. If the cancer diffusely involves the pancreas or is present at multiple sites within the pancreas, a total pancreatectomy may be required, where the surgeon removes the entire pancreas, part of the small intestine, a portion of the stomach, the common bile duct, the gallbladder, the spleen, and nearby lymph nodes. Patients with tumors in the head of the pancreas, who usually present because of

jaundice, are treated with open or laparoscopic pancreatoduodenectomy (ie, the Whipple procedure).^{358,359}

If the tumor is found to be unresectable during surgery, the panel recommends biopsy confirmation of adenocarcinoma at this time, if a biopsy was not performed previously. If a patient with jaundice is found to be unresectable at surgery, then the panel recommends stenting or biliary bypass at that time. In addition, gastrojejunostomy can be considered if appropriate regardless of jaundice (category 2B for prophylactic gastrojejunostomy). Celiac plexus neurolysis can also be performed, especially when indicated by pain in a patient with jaundice (category 2B for a non-jaundiced patient). See *Severe Tumor-Associated Abdominal Pain*, below, for more details about these procedures.

Pancreatoduodenectomy (Whipple Procedure)

Achievement of a margin-negative dissection must focus on meticulous perivascular dissection of the lesion in resectional procedures, recognition of the need for vascular resection and/or reconstruction, and the potential need for extra-pancreatic organ resection. Of course, the biology of the cancer might not allow for an R0 resection even with the most meticulous surgery.

Medial dissection of pancreatic head lesions is best achieved by complete mobilization of the PV and SMV from the uncinate process (assuming no evidence of tumor infiltration). Further, skeletonization of the lateral, posterior, and anterior borders of the SMA down to the level of the adventitia will maximize uncinate yield and radial margin (see Figure 1).^{360,361} Optimal dissection and skeletonization of the SMA can best be achieved utilizing fine dissection and suture ligation. Division of the retroperitoneal tissues between the uncinate process and the SMA with a stapler or a clamp and cut technique may leave up to 43% of the

soft tissue between the uncinate process and the SMA in situ and results in suboptimal clearance and increases the risk of an R1 resection.^{362,363}

The panel recommends analysis of the pancreatic neck and bile duct at time of surgery by frozen section. Frozen sections should be taken approximately 5 mm from the transection margin, with the clean cut side facing up, to avoid cautery artifact that may confound analysis and result in false negatives. If tumor is located within 5 mm of margins, further excision of the pancreas should be considered to ensure at least 5 mm of clearance.

In the absence of frank venous occlusion noted on preoperative imaging, the need for lateral venorrhaphy or complete PV or SMV resection and reconstruction to achieve an R0 resection may be suggested, but it is often not known until division of the pancreatic neck has occurred. Tethering of the carcinoma to the lateral wall of the PV is not uncommon and requires careful dissection to free the vein from the pancreatic head if it is possible to do so. Differentiation of tumor infiltration into the vein wall from tumor-related desmoplasia is frequently impossible to ascertain. The liberal use of partial or complete vein resection when vein infiltration is suspected during Whipple procedures has been studied.³⁶⁴⁻³⁶⁶ On evaluation of excised vein specimens, only 60% to 70% had histologic evidence of frank tumor involvement, and R0 resections were still not obtainable in 10% to 30% of patients despite increasing the magnitude of the operative procedure. However, if an R0 resection is obtained with vein excision, longevity appears similar to those with R0 resections without venous involvement, with no significant increase in morbidity and mortality. These data support an aggressive approach to partial or complete vein excision if tumor infiltration is suspected, although acceptance of this concept (particularly with respect to vein resection) is not universal.

Although numbers are more limited, similar findings have been noted with respect to hepatic arterial resection and reconstruction.^{366,367} Others, however, have noted poor short- and long-term outcomes with arterial resection.^{368,369} While further data with respect to arterial resection are clearly needed, judicious utilization of this technique would appear to be reasonable in very select populations.

A recent population-based study of 10,206 patients from the Nationwide Inpatient Sample from years 2000 through 2009 found that vascular reconstruction (about 90% venous and 10% arterial) is associated with a higher risk of intraoperative and postoperative complications.³⁶⁹ No difference in mortality was seen.

Distal Pancreatectomy

The goals of left-sided resection are similar to those of pancreatoduodenectomy, although they are often more difficult to achieve because of the advanced stage at which most of these cancers are discovered. Spleen preservation is not indicated in distal pancreatectomy for adenocarcinoma, and an R0 distal pancreatectomy for adenocarcinoma mandates en bloc organ removal beyond that of the spleen alone in up to 40% of patients.^{370,371} In addition, similar to the Whipple procedure, lateral venorrhaphy, vein excision and reconstruction, and dissection to the level of the celiac axis and SMA adventitia should be performed if complete tumor clearance can be achieved.^{371,372} Utilization of these radical resections is associated with an increase in blood loss, transfusion requirements, operating time, length of stay, and morbidity, but mortality remains rare.³⁷⁰⁻³⁷² Encouragingly, tumor clearance (R0 resection) has been reported in up to 72% to 91% of patients, with long-term survival equivalent to those having standard resection for more localized disease.^{371,372} Local recurrence, however, remains problematic even with pathologically negative margins.³⁷²

There is an increasing role for laparoscopic distal pancreatectomy. Results from 172 patients treated at the Mayo Clinic found significant benefits in the patients who had laparoscopic versus open resections in blood loss, the need for blood transfusions, and the length of hospital and intensive care unit stays without any difference in oncologic outcomes.³⁷³ In addition, results from a meta-analysis of 4 studies of 665 total patients suggest that the laparoscopic method is safe and results in shorter hospital stays.³⁷⁴ Furthermore, results from a population-based, retrospective cohort study that included 8957 patients showed similarly that the laparoscopic approach can decrease complication rates and shorten hospital stays.³⁷⁵

Portal Vein Resection

Vascular invasion has been a conventional contraindication to pancreatic resection. Early attempts at resection and reconstruction of the SMA and SMV in the 1970s were associated with poor results in a few patients who underwent “regional” pancreatectomy.³⁷⁶ Both autologous and synthetic grafts were used for arterial and venous reconstructions. As morbidity from pancreatoduodenectomy decreased, a subset of patients was identified who were in need of resection of the SMV wall to achieve negative margins during removal of their tumors. Thus, in the 1990s, there was renewed interest in vein resection for complete resections. The group from the University of Texas MD Anderson Cancer Center has championed this approach, demonstrating that vein resection and reconstruction can allow for complete resection and is not associated with increased morbidity or mortality when compared with patients who did not require vein resection.³⁷⁷ Furthermore, long-term outcome is not significantly worse for patients undergoing venous resection during pancreatoduodenectomy compared to patients who receive standard pancreatoduodenectomy.³⁷⁸

Although compelling, this approach has not been universally accepted. During the 1990s, several studies reported operative mortality of 0% to 16.5%, 3-year Kaplan-Meier survival of 12% to 23%, and median survival of 5 to 14 months in patients receiving vein resection.³⁷⁹⁻³⁸² One study found that properly selected patients with adenocarcinoma of the pancreatic head who required vein resection (n = 141) had a median survival of approximately 2 years that did not differ from those having standard pancreatoduodenectomy and was superior to historical patients believed to have locally advanced disease who did not receive surgical treatment.³⁶⁶ A meta-analysis of 22 retrospective studies (2890 patients) found that vein resection resulted in perioperative morbidity and mortality equal to that of standard resection, but R0 resection rates were lower in that group.³⁸³ In a recent multi-institutional database analysis of 492 patients undergoing pancreaticoduodenectomy, R0 resection rates were no different between the 14% who had vein resection compared to those without venous involvement (66% vs. 75%; $P = \text{NS}$).³⁸⁴ Nevertheless, a few groups have recommended caution and only use vein resection for selected patients.

Pylorus Preservation

Reconstruction options for the stomach after pancreatoduodenectomy center on preservation of the pylorus. Traverso and Longmire³⁸⁵ reported the modern use of pylorus preservation in 1978. The hypothesis was that preservation would improve emptying and provide nutritional benefit, but the benefits have been inconsistent to date. Yeo et al reported no adverse effects of pylorus preservation³⁸⁶; however, van Berge Henegouwen et al reported longer nasogastric drainage times.³⁸⁷ In several randomized and nonrandomized studies,³⁸⁸⁻³⁹³ the pylorus-preserving procedure seemed to be associated with shorter surgical duration. No consistent data suggest that pylorus preservation leads to a better quality of life or nutritional status in patients after

resection. Thus, pylorus-preserving pancreatoduodenectomy remains an unproven but certainly acceptable alternative to classic pancreatoduodenectomy performed with antrectomy.

Pancreatic Anastomosis

Efforts have focused on preventing pancreatic leaks and fistulas, which are morbid and potentially lethal complications of pancreatoduodenectomy. Pancreaticojejunostomy has traditionally been the standard reconstruction and is the major focus of morbidity and mortality after pancreatoduodenectomy because of leaks, abscess formation, and fistulas from this anastomosis. A randomized study at Johns Hopkins Hospital found no difference in fistula rates after pancreaticojejunostomy and pancreaticogastrostomy.³⁹⁴ However, a more recent multicenter, randomized, superiority trial compared the outcomes of 329 patients undergoing pancreaticoduodenectomy with either pancreaticojejunostomy or pancreaticogastrostomy.³⁹⁵ A significant difference was seen in the primary outcome measure of postoperative fistulas, which occurred in 19.8% of patients in the pancreaticojejunostomy group and 8.0% of patients in the pancreaticogastrostomy group (OR, 2.86; 95% CI, 1.38–6.17; $P = .002$). An increase in grade ≥ 3 a postoperative complications was seen, however, in the pancreaticogastrostomy group (24% vs. 21%). Criticisms of this trial have been published.³⁹⁶ Although a meta-analysis of 4 randomized controlled trials (676 patients) concluded that pancreaticogastrostomy is associated with a lower risk of fistula formation than pancreaticojejunostomy (RR, 0.41; 95% CI, 0.21–0.62),³⁹⁷ the optimal approach to anastomosis remains undefined.³⁹⁸

Surgeons have also examined various other options for the pancreaticojejunal anastomosis; end-to-end, end-to-side, duct-to-mucosa, and invaginating techniques have all proven to be safe and effective.^{399,400} Results of a prospective trial show that pancreatic fistula

can be almost entirely avoided by a technique that combines placement/tying of sutures under magnification with meticulous attention to blood supply.⁴⁰¹ Stents used in the 1930s and 1940s continue to be used today, but data suggest that they do not decrease leak rates.⁴⁰²

In addition to technical modifications, octreotide has been examined for its ability to decrease postoperative pancreaticojejunal leaks in patients undergoing pancreatic resections. However, octreotide did not decrease fistula rates when assessed in 2 prospective, randomized, double-blind, placebo-controlled studies (at the University of Texas MD Anderson Cancer Center and Johns Hopkins Hospital).^{403,404} Pasireotide, in contrast, significantly decreased the rate of grade ≥ 3 fistula, leak, or abscess in a single-center, double-blind, randomized controlled trial of 300 patients (9% in pasireotide group vs. 21% in placebo group; RR, 0.44; 95% CI, 0.24–0.78; $P = .006$).⁴⁰⁵ Finally, the use of fibrin glue sealant does not appear to decrease the rate of pancreatic fistulas.⁴⁰⁶

Extended Lymphadenectomy

The role of lymph node dissection as a component of pancreatoduodenectomy has been explored. In the 1970s and 1980s, pathology and autopsy studies demonstrated a high incidence of nodal metastasis (sometimes as high as 80%), leading some groups to propose a more aggressive lymphadenectomy in an attempt to regionally control disease.^{407,408} A standard lymphadenectomy in patients undergoing pancreatoduodenectomy entails removal of nodes at the duodenum and pancreas and on the right side of the hepatoduodenal ligament, the right side of the SMA, and the anterior and posterior pancreatoduodenal lymph nodes.⁴⁰⁹ An extended lymphadenectomy is most commonly performed in the United States by removing not only the nodes removed in the standard procedure, but also the soft tissue in the retroperitoneum from the hilum of the right

kidney to the left lateral border of the aorta on the right side, and from the PV to the origin of the inferior mesenteric artery on the left.⁴¹⁰

Several prospective, randomized trials have addressed the role of lymphadenectomy in patients undergoing pancreatoduodenectomy. The Italian Multicenter Lymphadenectomy Group reported on a series of 81 patients randomly assigned to pancreatoduodenectomy with or without extended lymph node resection. Although the statistical power was low, this study did not support the concept that an extended lymphadenectomy was a good prognostic factor.⁴¹¹ A larger randomized prospective trial was performed at Johns Hopkins Hospital from 1996 through 2001 to evaluate the role of extended lymph node dissections.⁴¹² The group of patients who received the regional lymphadenectomy in addition to pancreatoduodenectomy had longer operation times, but overall median survival did not differ between the 2 groups at 1, 3, and 5 years.⁴¹²⁻⁴¹⁴ Recently, a randomized multicenter trial in Japan came to similar conclusions.⁴¹⁵ Furthermore, multiple systematic literature reviews and meta-analyses of randomized controlled trials comparing pancreatoduodenectomy with standard versus extended lymphadenectomy support the conclusion that the extended procedure does not have any impact on survival.⁴¹⁶⁻⁴¹⁸ In addition, patients undergoing extended lymphadenectomy have increased rates of postoperative diarrhea compared to patients undergoing the standard resection.⁴¹⁹

The information to date thus does not show any survival advantage to performing a regional lymphadenectomy in addition to the standard pancreatoduodenectomy.⁴²⁰ At this point in time, data suggest that nodal metastases are a marker of systemic disease and that their removal is unlikely to alter OS. One exception might be in the situation of an otherwise R0 resection with clinically positive adenopathy outside the standard field of dissection. Overall, outside of a clinical trial, a

regional lymphadenectomy should not be considered as a routine part of the Whipple procedure, although consideration can be given to sampling of the aortocaval and common hepatic artery nodes, as those with positive nodes in these positions have inferior prognoses.^{421,422}

Preoperative Biliary Drainage

The main goals of preoperative biliary drainage are to alleviate the symptoms of pruritus and cholangitis and to potentially make surgery less morbid by improving liver function preoperatively. Although controversial, several studies have suggested that pancreatoduodenectomy is associated with higher perioperative mortality when done in the setting of hyperbilirubinemia.⁴²³⁻⁴²⁵ Stenting of the biliary system can improve symptoms and liver function, but it is not clear whether these changes can decrease the mortality rate of the Whipple procedure. Several prospective and retrospective studies have failed to show decreased mortality in patients with preoperative biliary drainage.⁴²⁶⁻⁴³² A retrospective analysis from a prospective database of 593 patients treated with pancreatoduodenectomy at MD Anderson Cancer Center found that self-expandable metal stents did not affect postoperative complications, 30-day mortality, length of stay, anastomotic leak, margin status, or determination of unresectability during resection, although more wound infections and longer operative times were observed in this group.⁴³³ In contrast, a multicenter, randomized trial comparing preoperative biliary drainage with surgery alone for 202 patients with cancer of the pancreatic head characterized by obstructive jaundice showed a nearly 2-fold increase in the rate of serious complications in the stented group (74% vs. 39%; relative risk in the surgery alone group, 0.54; 95% CI, 0.41–0.71; $P < .001$). However, no significant differences in surgery-related complications, length of hospital stay, or mortality were observed.⁴³⁴

Based on these reports, most groups who perform resection without neoadjuvant treatment advocate selective use of decompression only in patients who are symptomatic, septic, coagulopathic, have renal insufficiency, or in whom surgical resection is significantly delayed. The panel includes in this group patients who present with jaundice and potentially resectable disease if symptoms of cholangitis or fever are present or if they have significant pruritus and an expected delay to surgery of >1 week.

For patients with jaundice undergoing neoadjuvant induction therapy before pancreatic resection, biliary decompression is necessary before initiation of therapy and appears to be well tolerated with minimal increase in perioperative morbidity. The University of Texas MD Anderson Cancer Center reported on its experience with more than 300 patients, 57% of whom had preoperative biliary drainage as part of a neoadjuvant chemoradiation program.⁴³⁵ It was found that wound complications were significantly increased in the drainage group; however, no other association was found for sepsis, fistulae, or death. Placement of a stent is thus required prior to administration of neoadjuvant therapy for patients with jaundice.⁴³⁶⁻⁴³⁹

The panel notes that stents are an evolving technology. The choice of stents includes plastic and metal; fully covered, partially covered, or uncovered; rigid; or self-expanding (also see the discussion on stents in *Palliation and Supportive Care*, below). While any stent can become occluded, several groups have reported better patency with metal stents.⁴³⁷⁻⁴³⁹ Metal stents are generally viewed as more permanent than plastic stents. Covered metal stents may give more durable patency, since the cover prevents tumor ingrowth,⁴⁴⁰ but the reported differences between covered and uncovered stents are not dramatic.^{440,441} Furthermore, migration is more of an issue with covered stents.⁴⁴¹ This issue has led to the introduction of partially covered stents,⁴⁴² though

these stents may still migrate in a substantial number of patients.^{443,444} Most metal stents used today are self-expanding. Their small initial diameters make them easy to place, and their placement rarely requires dilation.⁴⁴² Several panel members reported that their institutions use plastic stents in patients with short life expectancies (<3 months).⁴⁴² A clinical trial is currently recruiting patients to compare metal and plastic stents for preoperative biliary decompression in patients with pancreatic cancer (ClinicalTrials.gov NCT01191814). In the absence of level-1 data, the panel consensus is that short, self-expanding, metal stents are preferred because they are easy to place without dilation, are unlikely to interfere with the subsequent resection, and have a longer patency time than plastic stents. The panel cautions against placement of a metal stent prior to tissue proof of malignancy.

Effect of Clinical Volume

Several studies have examined the effect of institutional volume on patient outcomes. The fundamental premise was that the decreasing morbidity and mortality seen in the 1980s and 1990s were the direct result of large, single-institution experiences. Moreover, the concern was that if surgeons performed pancreatoduodenectomy less frequently, patients might have increased morbidity and mortality. A group from Memorial Sloan Kettering Cancer Center examined the issue in 1995 and found that in a cohort of almost 2000 patients, high-volume centers in New York State had significantly less mortality than low-volume centers (4% vs. 12.3%).⁴⁴⁵ High volume was defined as more than 50 cases per year, and this relationship correlated in a regression analysis. Of note, 75% of the cases in New York State were performed in low-volume centers. Several other studies have assessed regional outcomes with pancreatoduodenectomy from U.S. hospitals.⁴⁴⁶⁻

⁴⁵⁰ These studies have reported decreased mortality, hospital length of stay, and overall cost at higher-volume centers (or with surgeons who

perform the resections frequently) when compared with low-volume centers. Interestingly, this effect was also seen in reports from Canada and the Netherlands.⁴⁵¹⁻⁴⁵³

The definitions of high and low volume varied among all these studies. However, a striking difference was seen when the mortality rates from pancreatoduodenectomy in very-low-volume (0–1 procedure/year) and low-volume (1–2 procedures/year) hospitals were compared with rates in higher-volume hospitals (>5 procedures/year).⁴⁵⁴ In-hospital mortality rates at these very-low-volume and low-volume hospitals were significantly higher than at high-volume hospitals (16% and 12%, respectively, vs. 4%; $P < .001$). The importance of hospital volume in improving survival after pancreatic cancer surgery is even more marked when pancreatoduodenectomy is compared to other major surgeries. In a retrospective analysis of data from the national Medicare claims database and the Nationwide Inpatient Sample, hospitals performing 6 to 16 and >16 procedures per year were classified as “high” and “very-high” volume centers.⁴⁵⁵ In this study, 6 or more pancreatic resections were performed at only 6.3% of hospitals. The largest difference in operative mortality between very-low-volume (16.3%) and high-volume (3.8%) centers was seen for pancreatoduodenectomy, as compared to major surgery at any other site, further reinforcing the magnitude of the effect that high-volume centers can have specifically on pancreatic cancer outcomes.

Furthermore, a study involving 301,033 patients with pancreatic adenocarcinoma included in the NCDB that evaluated the treatment patterns of 1667 hospitals over a 19-year period showed that patients were more likely to receive multimodality therapy at academic institutions considered to be high-volume hospitals.⁴⁵⁶ In addition, a recent systematic review showed that margin status correlates with hospital volume, with negative margin rates ranging from 55% in low-

volume centers to 76% for very-high-volume centers ($P = .008$).⁴⁵⁷ This review also found that 5-year survival rates were higher in high-volume centers. In contrast, hospital readmission after pancreatoduodenectomy appears to be more of a function of patient characteristics than hospital or surgeon volume.⁴⁵⁸

The NCCN Panel recommendation is that pancreatic resections should be done at institutions that perform a large number (at least 15–20) of pancreatic resections annually.

Pathology

Progress in treating pancreatic adenocarcinoma is encumbered by a lack of uniformity among treating physicians in defined areas that include pathologic analysis and reporting.⁴⁵⁹ A more standardized approach in this area could maximize the chances of a more complete and consistent pathology report that is similar among pathologists in the same institution and among institutions around the world. Ultimately, a more consistent approach to patient assessment, surgical technique, and pathologic evaluation of the resected pancreatic specimen from gross examination to pathologic report will provide better communication among the various treating physicians. It will also provide a clear and specific understanding of the individual patient's malignancy, including critical margin status, which will then allow a more accurate comparison of the existing and evolving treatment regimens for this lethal disease.

Specimen Orientation, Sectioning, Pathologic Analysis, and Reporting

The primary purpose of pathologic analysis of the pancreatic specimen is to determine the pathologic stage of the tumor by evaluating the type, grade, size, and extent of the cancer. Pathology synoptic reports (protocols) are useful for reporting results from examinations of surgical specimens; these reports assist pathologists in providing clinically

useful and relevant information. In 2004, the Commission on Cancer (CoC) of the American College of Surgeons mandated the use of specific checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. The pathology synoptic reports from the College of American Pathologists (CAP) comply with the CoC requirements, and the latest revisions to the CAP Pancreatic (Exocrine) protocol were issued in October 2013.⁴⁶⁰ The NCCN Pancreatic Adenocarcinoma Panel currently supports the CAP pathology synoptic reports. The proposal included in the guidelines (see *Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting* in the Guidelines) is an abbreviated *minimum* analysis of pancreatic cancer specimens from the CAP recommendations. In addition to the standard TNM staging, other variables are included, all of which have prognostic implications in the evolution of this disease.^{461,462}

Lymph Node Counts and Lymph Node Ratio

The CAP recommendations include a count of the number of lymph nodes recovered and the number of involved nodes.⁴⁶⁰ Recent retrospective database analyses have found that patients with N0 disease have a better prognosis with an increasing number of examined lymph nodes.^{463–465} These results suggest that a significant portion of patients with N0 disease might be understaged. Based on these data, groups have recommended the minimum number of lymph nodes examined to be from 11 to 17 to provide optimal staging and to serve as a quality indicator.^{463,465,466} The panel believes that every effort should be made to identify all regional lymph nodes within the pancreatectomy specimen.

For patients with N1 disease, lymph node ratio (positive node/nodes examined) appears to be related to prognosis.^{463–470} For instance, in one analysis, patients with <15% of examined positive nodes had a 5-year

survival rate of 21.7%, while those with >15% positive nodes had a 5.2% 5-year survival rate ($P = .0017$).⁴⁶⁸

Whipple Specimen

Specimen orientation and inking involves both a pathologist and surgeon, as this will help to ensure accurate assessment of the size and extent of the tumor. There should be either direct communication between the surgeon and pathologist for proper orientation and margin identification, or the surgeon should identify the important margins with a clearly understood and documented method (ie, written on the pathology requisition). For example, a stitch can be placed on the posterior margin and a safety pin on the retroperitoneal/uncinate margin.

One of the impediments to comparison of data across institutions is the variability in the names given to various margins. Definitions of the margins and uniformity of nomenclature are critical to accurate reporting. The panel's recommended definitions are included in the *Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting* section in the guidelines. Margins defined include the SMA (retroperitoneal/uncinate) margin, the posterior margin, the PV groove margin, the proximal and distal PV margins, the pancreatic neck (transection) margin, and the bile duct margin (see Figure 2). Other margins analyzed in Whipple specimens include the proximal and distal enteric margins (en face sections) and the anterior surface (closest representative). The anterior surface is not a true margin, but identification and reporting of this surface when positive may portend a risk of local recurrence, and so should be reported in all cases.^{459,471-473} Collectively, these pancreatic tissue surfaces constitute the circumferential transection margin. Designating the various specific margins with different colored inks will allow recognition on microscopy.

The approach to histologic sectioning of a Whipple specimen is determined by the unique characteristics of the tumor, but is also influenced by institutional preferences, expertise, and experience. There is no one correct way to dissect a Whipple specimen. Options include axial, bi- or multi-valve slicing, and perpendicular slicing (see Figure 3). Some experts in the field bisect the pancreas along probes placed in the bile and pancreatic ducts and then serially section along each half of the pancreas. Axial slicing provides an overall assessment of the epicenter of the tumor relative to the ampulla, bile duct, duodenum and pancreas, and all of the pancreatic circumferential tissue margins (see Figure 4).

The most important aspects of dissection are clear and accurate assessment of the margins. It is currently unknown what constitutes an adequate margin in pancreatic carcinoma resection specimens. A standardized definition of this would allow better stratification of patients into adjuvant regimens following surgical extirpation. For instance, if less than 1-mm clearance is associated with an unacceptably high incidence of local recurrence, then strong consideration for postoperative radiation therapy (RT) might be indicated if not received preoperatively. The panel strongly recommends reporting tumor clearance in millimeters for all margins (as noted in the *Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting* section of the guidelines) to allow prospective accumulation of these important data for future analysis.

A recent retrospective review compared the outcomes of 169 patients with R0 resections of close margins (within 1 mm) to 170 patients with wider margins (>1 mm) and found an improvement in OS with wider margins (35 months vs. 16 months; $P < .001$).⁴⁷⁴ In fact, the close-margin R0 patients had a median survival time similar to that of the R1 population (16 months vs. 14 months; $P = .6$). Consistent with these

results, another recent retrospective review of 285 patients found that those with R1 resections, defined as tumor ≤ 1 mm from the margin, had a significantly worse local recurrence-free survival than those with R0 resections (HR, 4.27; 95% CI, 2.07–8.81).^{475,476} Finally, a recent study, which used a standardized pathologic protocol that involved multicolor inking and careful evaluation of multiple margins distances, found that patients with R1 resections (tumor at 0 mm) had a median survival of 17.7 months, while those with R0 resections had a median survival of 32.9 months ($P = .10$).⁴⁷⁷ Together, these results suggest that an appropriate definition of a negative margin may be >1 mm.

Attached organs resected with the specimen en bloc require serial sectioning to assess not only direct extension, but metastatic deposits as well.

Distal Pancreatectomy Specimen

In left-sided resections, the peripancreatic soft tissue margins and the pancreatic neck are assessed (see Figure 5). Additionally, involvement of the splenic vessels should be documented, and invasion of the spleen is important to determine, because direct tumor invasion constitutes a pT3 pathologic stage. Frozen section analysis of the pancreatic neck is recommended. Definitions of the proximal pancreatic (transection) margin, the anterior (cephalad) peripancreatic (peripheral) surface, and the posterior (caudad) peripancreatic (peripheral) margin are included in the guidelines (see *Pathologic Analysis: Specimen Orientation, Histologic Sections, and Reporting* in the guidelines).

Perioperative Therapy

Even with R0 resections, recurrence rates are very high in this disease. Therefore, additional therapy is required for all patients with resected pancreatic adenocarcinoma.

Postoperative (Adjuvant) Therapy

Results of many trials have shown that adjuvant therapy improves outcomes over observation following resection (see sections on *Systemic Therapy Approaches* and on *Chemoradiation Approaches*, above). While results of RTOG 9704 cannot be directly compared with the results of the CONKO-001, ESPAC-1, or ESPAC-3 trials because of differences in treatment design, timing of imaging, and patient characteristics (eg, patients enrolled in CONKO-001 were more likely to be lymph node-negative and to have positive resection margins than those in RTOG 9704; and CONKO-001 excluded patients with high postoperative CA 19-9 or CEA levels¹⁹⁶), it is interesting to note that median OS for patients in the gemcitabine arm of CONKO-001 (22.8 months), the gemcitabine-containing arm of RTOG 9704 (20.5 months), the bolus 5-FU/leucovorin arm of ESPAC-1 (20.1 months), and the gemcitabine and 5-FU/leucovorin arms of the ESPAC-3 study (23.6 and 23.0 months) are remarkably similar.

Based on the data discussed above, no definite standard has been established in the adjuvant treatment of pancreatic cancer at this time. Gemcitabine- or fluoropyrimidine-based chemoradiation with additional gemcitabine, continuous infusion 5-FU, or 5-FU/leucovorin chemotherapy and chemotherapy alone with gemcitabine (category 1), 5-FU/leucovorin (category 1), or continuous infusion 5-FU are listed in the guidelines as options for adjuvant treatment. It was the consensus of the panel that when chemotherapy alone is the choice of adjuvant therapy, gemcitabine is preferred over 5-FU/leucovorin for most patients due to its more favorable toxicity profile. In the adjuvant setting, capecitabine monotherapy is also listed in the guidelines (category 2B). The panel considers capecitabine to be a reasonable alternative to 5-FU/leucovorin only in this setting as a last choice in patients for whom other options are inappropriate or unacceptable.

Regardless of the therapy being considered it is important to evaluate the patient for extent of disease prior to therapy, because some patients have early recurrence within the first few weeks following surgery. In addition, the panel recommends restaging a patient with imaging following systemic chemotherapy if chemoradiation is planned. While no studies have demonstrated superiority of giving chemoradiation before versus after chemotherapy in the adjuvant setting, when patients have a margin-positive resection, upfront chemoradiation followed by systemic chemotherapy is an appropriate option.

A recent retrospective analysis of data from patients in the ESPAC-3 trial found that completion of the full course of chemotherapy was an independent prognostic factor for survival, but that time to treatment initiation after surgery was not.⁴⁷⁸ These results suggest that delaying chemotherapy until patients adequately recover could possibly improve outcomes. The panel therefore recommends that adjuvant treatment be initiated within 12 weeks, after adequate recovery from surgery.

Ongoing clinical trials in the adjuvant setting include ESPAC-4 (www.controlled-trials.com/ISRCTN96397434), which is comparing gemcitabine with capecitabine to gemcitabine alone; RTOG 0848 (ClinicalTrials.gov NCT01013649), which is assessing gemcitabine with or without subsequent chemoradiation; a phase II study comparing FOLFIRINOX with albumin-bound paclitaxel (ClinicalTrials.gov NCT02243007); the APACT study (ClinicalTrials.gov NCT01964430), comparing albumin-bound paclitaxel with gemcitabine; and the IMPRESS trial, which is comparing gemcitabine (with or without chemoradiation) with and without algenpantucel-L immunotherapy (ClinicalTrials.gov NCT01072981).

Preoperative (Neoadjuvant) Therapy

The standard approach to therapy in patients with resectable disease has been postoperative treatment, with median survivals in the range of 20.1 to 23.6 months under the most optimal clinical trial conditions.^{196,240,241,268} However, it is becoming increasingly apparent that patients with borderline resectable disease, who are at higher risk for R1 resections, are potentially in need of a different management approach. Contemporary approaches to perioperative treatment have focused on neoadjuvant therapy for patients with borderline resectable disease with the goal of improving OS.^{337,340} Neoadjuvant therapy is also sometimes used in resectable patients, especially in those with high-risk features. The putative benefits of neoadjuvant therapy include increasing the likelihood that a higher proportion of resectable patients will receive chemotherapy and/or radiation; the potential to downsize tumors so as to increase the likelihood of a margin-free resection (ie, conversion to resectable status); the potential to select for surgery those patients with more stable disease or disease that is more responsive to therapy; and the treatment of micrometastases at an earlier stage.^{339,341,355,479} Moreover, surgery following neoadjuvant treatment appears to be safe.^{480,481}

EUS-FNA is the preferred method of obtaining histologic confirmation of disease, and such confirmation is necessary before administering neoadjuvant therapy. A repeat biopsy should be performed in cases where the initial biopsy results do not confirm cancer. In addition, staging laparoscopy, performed to evaluate for the possible presence of metastatic disease, can be considered before neoadjuvant therapy. Furthermore, patients for whom neoadjuvant therapy is planned should be assessed for jaundice, and placement of a stent (preferably a short, self-expanding metal stent, as discussed in *Preoperative Biliary Drainage*, above) is recommended prior to initiation of neoadjuvant therapy in patients with jaundice.⁴³⁷⁻⁴³⁹

There is insufficient evidence to recommend specific neoadjuvant regimens, and practices vary with regards to chemotherapy and chemoradiation. Acceptable regimens include FOLFIRINOX or gemcitabine/albumin-bound paclitaxel. Subsequent chemoradiation is sometimes included. Studies of these regimens without chemoradiation are in progress. The role of chemoradiation with more active chemotherapy regimens also needs to be tested.

Abdominal (pancreas protocol), pelvic, and chest imaging should be repeated following neoadjuvant therapy, and staging laparoscopy can be considered at this time if not previously performed. Surgical resection should only be attempted if there is a high likelihood of achieving an R0 resection. Surgery is ideally performed 4 to 8 weeks after therapy. Surgery can be performed more than 8 weeks following therapy, but radiation-induced fibrosis may potentially make surgery more difficult. Importantly, results from retrospective studies suggest that radiographic response does not correlate with pathologic response.^{482,483} Therefore, if no apparent tumor shrinkage is observed after neoadjuvant treatment and no extrapancreatic progressive disease is evident, surgery should still be attempted.

Neoadjuvant Therapy in Borderline Resectable Disease

Patients with borderline resectable disease have the options of upfront resection (category 2B) with adjuvant therapy or neoadjuvant therapy followed by restaging and resection in patients without disease progression precluding surgery. The use of neoadjuvant therapy in the setting of borderline resectable disease has been a highly debated topic. However, although there is no high-level evidence supporting its use, most NCCN Member Institutions now prefer an initial approach involving neoadjuvant therapy, as opposed to immediate surgery, for patients with borderline resectable disease. In fact, the panel down-

graded its recommendation for upfront resection in borderline cases to category 2B in the 2014 version of these guidelines.

Several trials have shown that preoperative treatment of borderline resectable pancreatic adenocarcinoma can be effective and well-tolerated.⁴⁸⁴⁻⁴⁸⁹ A phase I/II trial of neoadjuvant therapy in borderline resectable disease allowed 4 of 26 patients (15%) to be resected.⁴⁸⁸ A randomized phase II trial comparing 2 different neoadjuvant regimens in borderline resectable disease was terminated early due to poor accrual, but 5 of 21 patients (24%) were resected.⁴⁸⁷ A recent multi-institutional phase II trial found that full-dose gemcitabine, oxaliplatin, and radiation given preoperatively to patients with resectable (n=23), borderline resectable (n=39), or unresectable disease (n=6) found the approach to be feasible with an overall R0 resection rate of 53%.⁴⁸⁶ In this study, 63% of all evaluable patients underwent resection, with 84% of those patients achieving an R0 resection.

In 2 retrospective reviews, 31% to 35% of borderline resectable patients who completed neoadjuvant therapy had R0 resections.^{490,491} A systematic review and meta-analysis of 19 cohort studies found that unresectable patients (including both borderline and unresectable patients) undergoing neoadjuvant chemoradiation therapy had similar 1-year survival outcomes as patients who were initially deemed resectable.⁴⁹² In this study, 40% of treated patients were ultimately resected.

It is important to note that no randomized phase III trials have compared the approach of neoadjuvant therapy in borderline resectable disease compared to the approach of taking these patients to surgery without initial therapy, and the best regimens to use in the borderline neoadjuvant setting are unknown. Several phase II clinical trials are currently underway to determine the R0 resection rate following

neoadjuvant chemotherapy in patients with borderline resectable or unresectable locally advanced disease (eg, ClinicalTrials.gov NCT00557492). In addition, the Alliance A021101 trial (NCT01821612) is a single-arm pilot study evaluating the safety and efficacy of FOLFIRINOX before capecitabine-based chemoradiation and surgery in this population.³⁵⁶ Initial results in patient series suggest that neoadjuvant regimens including FOLFIRINOX are a promising approach in patients with borderline resectable disease.^{493,494} Additional randomized trials are needed.

Neoadjuvant Therapy in Resectable Disease

A number of studies have evaluated the use of neoadjuvant chemoradiation in patients with resectable disease.^{339,340,495-503} A retrospective review of the collective experience at the University of Texas MD Anderson Cancer Center suggested that the use of preoperative chemoradiation therapy in patients with resectable disease is advantageous.⁴⁹⁶ The authors suggest that preoperative therapy gives a selection advantage because approximately 25% of patients who are restaged after therapy are found to have progressive disease and are therefore spared the morbidity of a surgical procedure that would not benefit them.⁴⁹⁶ In this analysis of 132 consecutive patients, the authors reported that combined preoperative chemoradiation and pancreatoduodenectomy yielded a median survival of 21 months, and 32% of patients were alive without evidence of disease at a median follow-up of 14 months.⁴⁹⁶ The MD Anderson group has continued to champion this approach both for its ability to select patients for resection and for cost-effectiveness.⁵⁰⁴ Other potential advantages of the neoadjuvant approach in resectable patients have also been described, including sterilization of the field before resection potentially reducing spread during surgery; increased rates of R0 resections; decreased incidence of pancreatic fistulas; prevention of delays or

reductions of adjuvant therapy after surgery; and improved delivery of chemotherapy and radiosensitizing oxygenation.^{481,505,506}

Although most studies investigating the neoadjuvant experience in patients with resectable pancreatic cancer are retrospective, several small phase II studies have been published.^{481,505,507,508} In a randomized phase II trial evaluating the safety and efficacy of gemcitabine-based chemotherapy regimens as neoadjuvant therapy for patients with resectable pancreatic cancer, more patients receiving gemcitabine with cisplatin were able to undergo resection compared with those in the gemcitabine-only arm.⁵⁰¹

In a prospective trial, preoperative radiation with concurrent gemcitabine was administered to 86 patients with resectable disease, and patients were restaged 4 to 6 weeks following completion of neoadjuvant treatment.⁴⁹⁸ Although all patients were able to complete neoadjuvant therapy, at the time of restaging, only 73 (85%) patients were able to undergo surgery; the majority of the remaining patients were precluded from undergoing a pancreatoduodenectomy due to the presence of more advanced disease. Similar results were observed in another phase II trial involving preoperative gemcitabine/cisplatin followed by gemcitabine-based chemoradiation.⁴³⁸ In this study, which enrolled 90 patients, 79 patients were able to complete neoadjuvant therapy, and 52 patients underwent surgery. Again, the main reason patients were precluded from surgery was the finding of more advanced disease at restaging following completion of neoadjuvant therapy. A cross-study comparison of these results suggests that inclusion of preoperative chemotherapy prior to initiation of gemcitabine-based chemoradiation did not improve survival.⁴⁷⁹ These results provide support for restaging patients with abdominal (pancreas protocol), pelvic, and chest imaging and diagnostic laparoscopy before committing them to laparotomy after neoadjuvant therapy.

Although evidence suggests that there may be a better chance of margin-negative resection with preoperative therapy,⁵⁰⁹ results of randomized trials addressing this issue are needed. A recent randomized phase II trial, which was terminated early because of slow accrual, compared gemcitabine/cisplatin neoadjuvant chemoradiation with upfront surgery; both arms received adjuvant chemotherapy.⁵¹⁰ With only 66 patients eligible for analysis, no significant differences were seen in R0 resection rate (52% vs. 48%), (y)pN0 rate (39% vs. 30%), or OS (25.0 months vs. 18.9 months), although all results favored the neoadjuvant arm and no safety issues were noted. The phase III NEOPA trial, with OS as the primary endpoint, is currently recruiting patients with resectable pancreatic cancer to compare neoadjuvant gemcitabine chemoradiation therapy to upfront surgery in this population (ClinicalTrials.gov NCT01900327).⁵¹¹ A phase II trial with R0 resection as the primary endpoint is also ongoing (ClinicalTrials.gov NCT01389440).

At this time, the panel does not recommend neoadjuvant therapy for most resectable patients, except in a clinical trial. For selected patients who appear technically resectable but have poor prognostic features (ie, borderline resectable disease; markedly elevated CA 19-9; large primary tumors; large regional lymph nodes; highly symptomatic), however, consideration can be given to neoadjuvant therapy after biopsy confirmation, although a clinical trial is still preferred.

Adjuvant Treatment After Neoadjuvant Therapy

For patients who received neoadjuvant treatment, data supporting additional therapy after surgery are lacking. The consensus of the panel is that patients who have received neoadjuvant chemoradiation or chemotherapy may be candidates for additional chemotherapy following surgery and multidisciplinary review. When chemotherapy is given, the

choice of regimen may be based on response seen to neoadjuvant therapy.

Adjuvant chemotherapy or adjuvant chemoradiation should only be considered for pre-treated patients who have adequately recovered from surgery and have no evidence of recurrence or metastatic disease; treatment should ideally be initiated within 4 to 8 weeks. It is recommended that the patient undergo a pretreatment baseline assessment following surgery, including CT scan and CA 19-9 level, to evaluate for the presence of metastatic disease before adjuvant chemoradiation is initiated. Further, the panel recommends restaging a patient with imaging following systemic chemotherapy, if it will precede chemoradiation.

Surveillance of Resected Patients

Although data on the role of surveillance in patients with resected pancreatic adenocarcinoma are very limited,⁵¹²⁻⁵¹⁴ recommendations are based on the consensus that earlier identification of disease may facilitate patient eligibility for investigational studies or other forms of treatment. The panel recommends history and physical examination for symptom assessment every 3 to 6 months for 2 years, then annually. CA 19-9 determinations and follow-up CT scans every 3 to 6 months for 2 years after surgical resection are category 2B recommendations, because data are not available to show that earlier treatment of recurrences, following detection by increased tumor marker levels or CT scan, leads to better patient outcomes. In fact, a recent analysis of the SEER-Medicare database showed no significant survival benefit for patients who received regular surveillance CT scans.⁵¹⁵

Management of Recurrent Disease After Resection

As cross-sectional body imaging has improved, small-volume metastatic disease or local recurrence is being detected in patients with resected pancreatic cancer who are otherwise maintaining good functional status. As many as 50% of them will continue to maintain a sufficiently good performance status to consider second-line therapy.⁵¹⁶ These patients will, however, ultimately progress.

For patients experiencing a recurrence of disease following resection, the panel recommends consideration of confirmatory biopsy (category 2B). In all cases of recurrent disease, a clinical trial is the preferred option; palliative and best supportive care without additional therapy should also be an option, especially for patients with poor performance status. Alternatively, chemoradiation can be considered in patients with local disease recurrence only, if not previously administered, or an alternative chemotherapy regimen can be given. For patients for whom there is evidence of metastatic disease (with or without a local recurrence), treatment decisions are influenced by the length of time from completion of adjuvant therapy to the detection of metastases. If adjuvant therapy was completed less than 6 months prior to development of metastatic disease, the panel recommends that an alternative chemotherapy option be administered. When this period is greater than 6 months, systemic therapy as previously administered or an alternative systemic regimen is recommended. Recommended regimens for patients with previous adjuvant treatment and good performance status are gemcitabine/albumin-bound paclitaxel and FOLFIRINOX.

Management of Isolated Pulmonary Metastases

Some patients have isolated lung metastases after resection of localized pancreatic adenocarcinoma. A growing body of evidence in

this population suggests that these patients have a prolonged survival compared to patients with metastases in other locations.^{517,518}

Preliminary data also suggest that pulmonary metastasectomy may be advantageous in this population.⁵¹⁹ More data are needed before recommendations can be made regarding the management of pulmonary metastases of pancreatic cancers.

Palliative and Supportive Care

A significant subset of patients with pancreatic cancer will require substantial palliative interventions that are, in many respects, unique to the disease. The multidisciplinary management of symptoms due to biliary obstruction, gastric outlet obstruction, and cancer-related pain is of primary importance. The main objective of palliative care is to prevent and ameliorate suffering while ensuring optimal quality of life. Palliative surgical procedures are best reserved for patients with longer life expectancies.

Biliary Obstruction

Approximately 65% to 75% of patients with pancreatic cancer develop symptomatic biliary obstruction.⁵²⁰ For patients diagnosed with unresectable disease and biliary obstruction upon initial evaluation, the best palliation is provided by an endoscopic biliary stent, especially when anticipated survival is limited. In most cases, a permanent self-expanding metal stent (SEMS) is recommended unless biliary bypass is performed (also see the discussion on stents in *Preoperative Biliary Drainage*, above). Stent occlusion that causes recurrent cholangitis is a well-known complication of plastic (temporary) biliary stents and typically occurs within 3 months of insertion. Metal stents are wider in diameter than plastic stents (ie, less likelihood of blockage) and become embedded in the bile duct, whereas plastic stents are more likely to become occluded but can be replaced. Results of a randomized,

controlled trial of 100 patients at a single center randomly assigned to receive either a plastic stent or a covered self-expanding metal stent inserted endoscopically indicated that median patency times were 1.8 and 3.6 months ($P = .002$), respectively.⁵²¹ A meta-analysis comparing metal and plastic biliary stents placed endoscopically in patients with pancreatic adenocarcinoma characterized by biliary obstruction showed similar results.⁵²² This study suggested that the risk of recurrent biliary obstruction was lower for the metal stents (RR, 0.52; 95% CI, 0.39–0.69), although no significant differences in technical/therapeutic success, complications, or 30-day mortality were found. Another recent randomized trial showed that covered SEMS had longer patency than uncovered SEMS in the setting of biliary obstruction due to pancreatic cancer, because covered stents prevented the ingrowth of tumor.⁵²³

When a biliary stent cannot be placed (often because the endoscope cannot be advanced past the neoplasm that is obstructing the gastric outlet), percutaneous biliary drainage with subsequent internalization may be necessary. An alternative is to sequentially dilate the duodenum endoscopically, place a metallic biliary stent, and then place an enteral stent.⁵²⁴ Durable palliation of biliary obstruction can often be achieved with an expandable metallic biliary endoprosthesis (eg, Wallstent, Boston Scientific) in this situation.⁵²⁴

For patients with jaundice and potentially resectable disease who are found to have unresectable tumors following laparotomy, an open biliary-enteric bypass provides durable palliation of biliary obstruction and can be combined with procedures that palliate symptoms resulting from gastric outlet obstruction and cancer-related pain. The panel recommends stenting or an open biliary-enteric bypass with or without gastrojejunostomy (category 2B for prophylactic gastrojejunostomy^{525,526}) and with or without celiac plexus neurolysis⁵²⁷⁻⁵²⁹ (category 2B in non-jaundiced patients). Please see *Gastric Outlet*

Obstruction and Severe Tumor-Associated Abdominal Pain below for more detailed information on these procedures. Bypass of the common bile duct (choledochojejunostomy) or common hepatic duct (hepaticojejunostomy) to the jejunum is preferred to bypass of the gallbladder (cholecystojejunostomy) since choledochojejunostomy/hepaticojejunostomy provide more durable and reliable palliation of biliary obstruction.⁵²⁰

Biliary decompression is also required for jaundiced patients with disease progression precluding surgery with or without neoadjuvant therapy. Here, stenting or biliary bypass is recommended, with or without gastrojejunostomy (category 2B for prophylactic gastrojejunostomy^{525,526}) and with or without celiac plexus neurolysis (category 2B). One final circumstance requiring biliary drainage is in jaundiced patients with locally advanced or metastatic disease (those for whom surgical resection will not be attempted). In this situation, a SEMS is preferred unless biliary bypass was performed at the time of laparoscopy or laparotomy. If cancer has not been biopsy-confirmed in the setting of locally advanced disease in a jaundiced patient, brushings can be obtained at the time of stent placement.

Gastric Outlet Obstruction

Symptomatic gastric outlet obstruction occurs in 10% to 25% of patients with pancreatic cancer.⁵²⁰ Patients with locally advanced or metastatic disease and a short life expectancy or poor performance status who develop gastric outlet obstruction may be palliated with an endoscopically placed enteral stent after biliary drainage is assured.⁵²⁴ An alternative for these patients with poor performance status is percutaneous endoscopic gastrostomy (PEG) tube placement. For a fit patient with a life expectancy greater than 3 to 6 months (ie, locally advanced disease) who develops gastric outlet obstruction, an open or

laparoscopic gastrojejunostomy (duodenal bypass) with or without a jejunostomy (J) tube should be considered since it may provide more durable and effective palliation of gastric outlet obstruction than an enteral stent.⁵³⁰⁻⁵³² Nevertheless, placement of an enteral stent is also an option for these patients.

For patients with potentially resectable disease who undergo a laparotomy and are found to have unresectable disease, a prophylactic gastrojejunostomy should be performed for those deemed to be at risk of developing symptomatic gastric outlet obstruction (category 2B). The role of prophylactic gastrojejunostomy in otherwise asymptomatic patients who are found to have unresectable cancers at the time of laparotomy has been evaluated. Two randomized controlled trials have investigated the role of prophylactic gastrojejunostomy for unresectable periampullary cancer, the majority arising from the head of the pancreas.^{525,526} In both studies, approximately 20% of patients who did not undergo a prophylactic gastrojejunostomy developed late gastric outlet obstruction that required therapy. A recent meta-analysis found similar results, with development of gastric outlet obstruction in 2.5% of patients in the prophylactic gastrojejunostomy group and 27.8% of those not receiving gastrojejunostomy.⁵³³ In both studies, prophylactic retrocolic gastrojejunostomy significantly decreased the incidence of late gastric outlet obstruction but did not extend the length of stay or increase complication rates, such as delayed gastric emptying.

Severe Tumor-Associated Abdominal Pain

Most patients with locally advanced or metastatic pancreatic cancer experience cancer-related pain.⁵²⁹ General principles for cancer-related pain management can be found in the NCCN Guidelines for Adult Cancer Pain (available at www.NCCN.org). Because advanced pancreatic cancer often infiltrates the retroperitoneal nerves of the

upper abdomen, celiac plexus neurolysis should be considered for pain. In several randomized controlled trials, celiac plexus neurolysis significantly improved pain relief in patients with advanced pancreatic cancer.^{527,529,534} In a recent study of 96 patients with pain related to suspected pancreatic cancer, half were randomized to EUS-guided celiac plexus neurolysis at the time of EUS if unresectable adenocarcinoma was confirmed.⁵²⁸ These patients reported better pain relief at 3 months ($P = .01$), suggesting that early EUS-guided celiac plexus neurolysis may be beneficial. A recent meta-analysis of 7 randomized controlled trials concluded that celiac plexus neurolysis improved pain scores at 4 weeks but not at 8 weeks in patients with pancreatic cancer.⁵³⁵

Minimally invasive techniques including EUS-guided (preferred if available) and percutaneous fluoroscopic- or CT-guided celiac plexus neurolysis are recommended, but laparoscopic, thoracoscopic, and open approaches can also be used. In patients with pain found to be unresectable at surgery, celiac plexus neurolysis can be performed intraoperatively; the procedure is sometimes also performed prophylactically at the time of surgery in patients without pain who are found to be unresectable (category 2B).

In selected patients with severe local back pain refractory to narcotic therapy, palliative RT may be considered, even in the setting of metastatic disease, if not already given as part of primary therapy. In such cases, radiation is given with or without concurrent chemotherapy to the primary tumor plus a margin (typically 25–36 Gy in 2.4–5 Gy fractions), or radiation alone is given to the metastatic site.

Pancreatic Exocrine Insufficiency

Exocrine enzyme insufficiency in pancreatic cancer is caused by tumor-induced damage to the pancreatic parenchyma and/or blockage of the

pancreatic duct, or by surgical removal of pancreatic tissue, and results in an inadequate production of digestive enzymes.^{536,537} This deficiency in pancreatic enzymes results in inadequate absorption of fat, carbohydrates, and proteins, leading to steatorrhea, abdominal cramps, weight loss, and malnutrition.⁵³⁸ Oral pancreatic exocrine enzyme replacement therapy is recommended for patients with pancreatic cancer who have symptoms of exocrine enzyme deficiency. Because pancreatic exocrine insufficiency occurs in up to 94% of patients undergoing pancreatic surgery,^{539,540} therapy may be initiated without diagnostic tests. Enteric-coated mini-microspheres containing preparations of pancreatic enzymes are taken orally (25,000–75,000 units of lipase for a main meal and 10,000–25,000 units of lipase for a snack, depending on fat content), with half of the dose taken at the start of the meal and half taken in the middle of the meal.⁵³⁸ For patients not responding to this therapy, doses of the enzyme preparation can be increased, and inhibition of gastric secretion with a proton pump inhibitor can also be considered.^{538,539} Patients with a clinical suspicion of pancreatic exocrine insufficiency despite appropriate replacement may need a more thorough nutritional evaluation.

Thromboembolic Disease

The risk of developing venous thromboembolic disease is substantially increased in patients with pancreatic cancer.^{541,542} The panel recommends low-molecular-weight heparin (LMWH) as preferred therapy over warfarin for patients with pancreatic cancer who develop a venous thromboembolism (VTE). Support for this recommendation comes from results of 2 large, prospective, randomized clinical trials: CLOT and CONKO 004. In the CLOT study, an approximately 2-fold decrease in the incidence of recurrent VTE at 6 months was observed in patients with advanced or metastatic cancer diagnosed with a VTE who were treated with the LMWH, dalteparin, compared with those

treated with an oral anticoagulant.⁵⁴³ In the CONKO 004 trial, VTE- and chemotherapy-naïve patients with advanced pancreatic cancer were randomized to receive palliative chemotherapy with or without the LMWH, enoxaparin.⁵⁴⁴ The risk of developing symptomatic VTE was significantly lower for patients in the LMWH arm of the study with no significant increase in bleeding observed in this group compared to those not receiving enoxaparin. Please see the NCCN Guidelines for Venous Thromboembolic Disease, available at www.NCCN.org, for more information.

Depression, Pain, and Malnutrition

For many patients, a diagnosis of pancreatic cancer may result in significant psychosocial distress, including anxiety, depression, and sleep disturbances.⁵⁴⁵ In fact, the suicide rate in male patients with pancreatic cancer is reportedly 11 times that of the general population.⁵⁴⁶ Empathetic discussion about the natural history of this disease and its prognosis and the provision of support and counseling both by the primary oncology team and specialized services may help to alleviate this distress. The panel recommends that patients be screened and evaluated for depression and other psychosocial problems following the NCCN Guidelines for Distress Management (available at www.NCCN.org).

Because pain and malnutrition are also prevalent in patients with pancreatic cancer, the panel recommends that patients with locally advanced or metastatic pancreatic cancer receive a nutritional evaluation and a formal evaluation by a Palliative Medicine Service, when appropriate. Additional resources are detailed in the NCCN Guidelines for Palliative Care and the NCCN Guidelines for Adult Cancer Pain (available at www.NCCN.org).

Future Clinical Trials: Recommendations for Design

In 2007, a meeting was convened by the National Cancer Institute's Gastrointestinal Cancer Steering Committee in recognition of the failure of a number of phase III trials to show clinically significant benefit for patients with pancreatic cancer and to address the importance of integrating basic and clinical knowledge in the design of clinical trials in pancreatic cancer. Meeting participants included representatives from industry, government, and the community, as well as academic researchers and patient advocates. Several important themes emerging from this meeting are summarized below, and the recommendations put forward by the committee are endorsed by the NCCN Pancreatic Adenocarcinoma Panel.⁵⁴⁷

- With the emergence of new agents to treat pancreatic cancer, particularly biologics, clinical trial strategies incorporating principles of molecular biology and new imaging methods as well as results from preclinical studies are important.
- For patients enrolled in clinical trials, banking of tumor tissue samples should be required along with paired blood and serum samples.
- Biomarkers that serve as surrogate markers of the anticancer effects of investigational agents should be sought, and assays to measure such biomarkers should be well validated.
- Clinical trials should enroll homogeneous patient populations with respect to disease stage (ie, separate trials for patients with locally advanced disease and metastatic disease) and patient performance status. Criteria for selecting study populations should take into account the putative differential efficacy of the agent (ie, vaccines in patients with early-stage disease).

- Phase III trials should not be initiated in the absence of clinically meaningful efficacy and safety signals in the phase II setting.
- Phase II and III clinical trials should have a primary endpoint of OS.
- Quality control standards for preoperative imaging interpretation, pathologic assessment of tumor specimens, and surgical selection criteria are critical when evaluating adjuvant therapies.

A 2011 consensus report from a group of European experts came to many of the same conclusions.⁵⁴⁸ Additionally, the group states that FOLFIRINOX can be considered as a new standard treatment option in selected patients in future clinical trials, but that gemcitabine should remain the standard for most patients. An international expert panel also met to discuss current and future pancreatic cancer research and came to similar conclusions.⁵¹⁶ In addition, the Intergroup Pancreatic Cancer Task Force's Tissue Acquisition Working Group has made recommendations regarding the prospective collection and sharing of tissue to accelerate the discovery of predictive and prognostic biomarkers.⁵⁴⁹ These recommendations include centralization of biorepositories and mandatory collection of tissue (when there is sufficient material), blood, serum, and plasma in all phase III trials.

ASCO also recently convened a working group to discuss designs for pancreatic cancer clinical trials that would accomplish meaningful clinical improvements.⁵⁵⁰ This group concluded OS should be the primary endpoint of first-line, metastatic pancreatic cancer trials. They also concluded that trials should aspire to a 3- to 4-month improvement in OS in gemcitabine-eligible and gemcitabine/albumin-bound paclitaxel-eligible patients and a 4- to 5-month improvement in



OS for FOLFIRINOX-eligible patients to give results with true clinical impact.

To determine appropriate historic controls for single arm phase II trials based on gemcitabine, an algorithm has been developed, based on an analysis of a database of cooperative group trials, that can be used to calculate historic benchmarks for OS and PFS.⁵⁵¹

Neoadjuvant Clinical Trials

For neoadjuvant trials, study populations should be well defined and standardized. The panel endorses use of a restrictive definition of borderline resectable disease in clinical trials, such as that defined in a recent Intergroup trial.³⁵⁶ Endpoints should also be standardized and could include resection rates, R0 resection rates, local recurrence rates, pathologic response rates, DFS, and OS.⁵⁵²

Summary

Resection remains the only chance for a cure for pancreatic adenocarcinoma, and most resectable patients should undergo surgery without delay, followed by adjuvant therapy. Borderline resectable patients and select resectable patients can undergo neoadjuvant

therapy in the hopes of improving the chances for an R0 resection or can immediately undergo surgery (category 2B). Additional therapy is an option for those patients whose disease recurs following surgery. Patients with locally advanced unresectable disease and good performance status can undergo chemotherapy and chemoradiation with second-line therapy if performance status is maintained after progression. Good performance status patients presenting with metastatic disease can undergo chemotherapy and can undergo second-line therapy if performance status is maintained after progression. Specific palliative measures are recommended for patients with advanced pancreatic adenocarcinoma characterized by biliary or gastric obstruction, severe abdominal pain, or other tumor-associated manifestations of the disease.

Overall, in view of the relatively high likelihood of poor outcomes for patients with all stages of pancreatic cancer, the NCCN Panel recommends that investigational options be considered in all phases of disease management.

Table 1: Selected Genetic Syndromes with Associated Pancreatic Cancer Risk

Syndrome	Gene	Estimated cumulative risk of pancreatic cancer	Estimated increased risk compared to general population
Peutz-Jeghers Syndrome	<i>STK11</i>	11%–36% by age 65–70 years ⁵⁹	132-fold ⁵⁸
Familial Pancreatitis	<i>PRSS1</i> , <i>SPINK1</i> , <i>CFTR</i>	40%–53% by age 70–75 years ^{63–65}	26-fold to 87-fold ^{29,63–65}
Melanoma-Pancreatic Cancer Syndrome	<i>CDKN2A</i>	17% by age 75 years ⁶⁸	20-fold to 47-fold ^{67,68}
Lynch Syndrome	<i>MLH1</i> , <i>MSH2</i> (<i>MSH6</i>)	4% by age 70 years ⁷⁷	9-fold to 11-fold ^{77,78}
Hereditary Breast-Ovarian Cancer Syndrome	<i>BRCA1</i> , <i>BRCA2</i>	1.4%–1.5% (women) and 2.1%–4.1% (men) by age 70 ^{79,84}	2.4-fold to 6-fold ^{79,83,84}
Familial Pancreatic Cancer	Unknown in most families (family X is an exception)*	<p>≥3 first-degree relatives with pancreatic cancer: 7%–16% by age 70⁵¹</p> <p>2 first-degree relatives with pancreatic cancer: 3% by age 70⁵¹</p>	<p>≥3 first-degree relatives with pancreatic cancer: 32-fold⁹⁰</p> <p>2 first-degree relatives with pancreatic cancer: 6.4-fold⁹⁰</p> <p>1 first-degree relative with pancreatic cancer: 4.6-fold⁹⁰</p>

*One family (family X) with a mutation in the *palladin* (*PALLD*) gene has been identified.⁵⁵³

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Pancreatic Adenocarcinoma

Table 2: Potential Indications for Various Therapies in the Treatment of Pancreatic Adenocarcinoma

Regimen	Resectable (adjuvant)	Borderline Resectable (neoadjuvant)	Locally Advanced	Metastatic (good performance status)
Gemcitabine	√ (category 1)		√ (category 1 for poor performance status)	√ (category 1 for good and poor performance status)
Gemcitabine/Albumin-Bound Paclitaxel		√	√	√ (category 1; preferred)
Gemcitabine/Erlotinib			√	√ (category 1; survival benefit is small)
Gemcitabine/Cisplatin			√ (especially if possible hereditary cancer)	√ (especially if possible hereditary cancer)
Gemcitabine/Capecitabine			√	√
Fixed-dose-rate gemcitabine			√	√ (category 2B)
GTX [Fixed-dose-rate gemcitabine/docetaxel/capecitabine]			√ (category 2B)	√ (category 2B)
5-FU/Leucovorin	√ (category 1)			
FOLFIRINOX		√	√	√ (category 1; preferred)
Capecitabine	√ (category 2B)		√ (category 2B)	√ (category 2B)
Continuous Infusion 5-FU	√		√ (category 2B)	√ (category 2B)
Fluoropyrimidine/Oxaliplatin (eg, FOLFOX, CapeOx)			√ (category 2B)	√ (category 2B)
Radiation	√ (fluoropyrimidine- or gemcitabine- based)	√ (subsequent chemoradiation is sometimes included)	√ (in select patients without systemic metastases; fluoropyrimidine- or gemcitabine-based)	√ (palliative only)

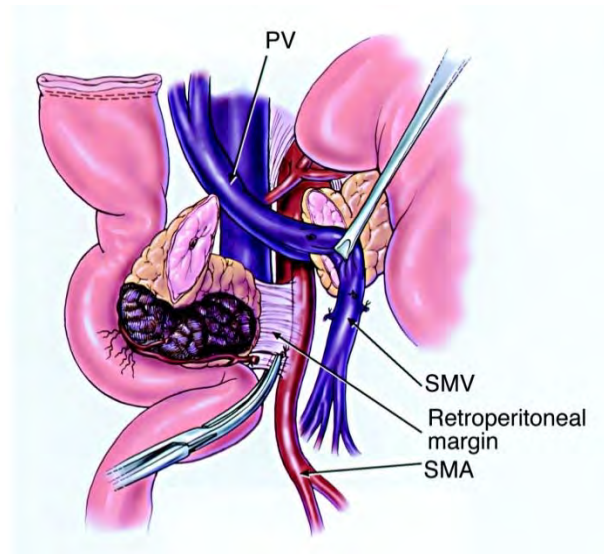


Figure 1. Complete mobilization of the superior mesenteric (SMV) and portal veins, and separation of the specimen from the right lateral border of the superior mesenteric artery (SMA).⁵⁵⁴

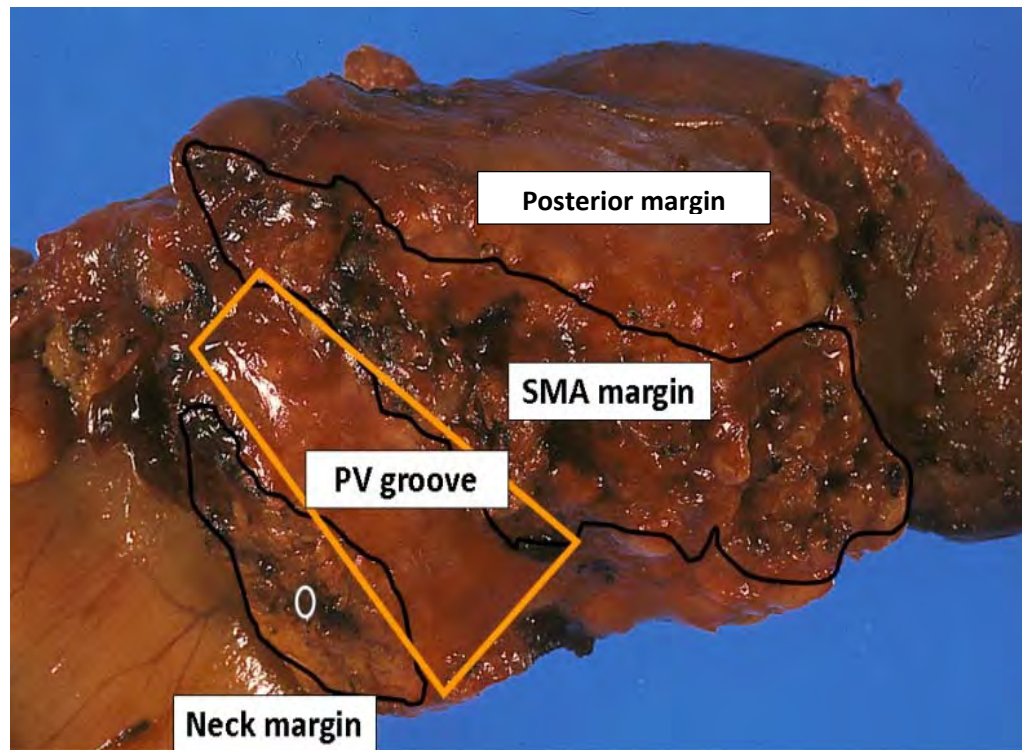
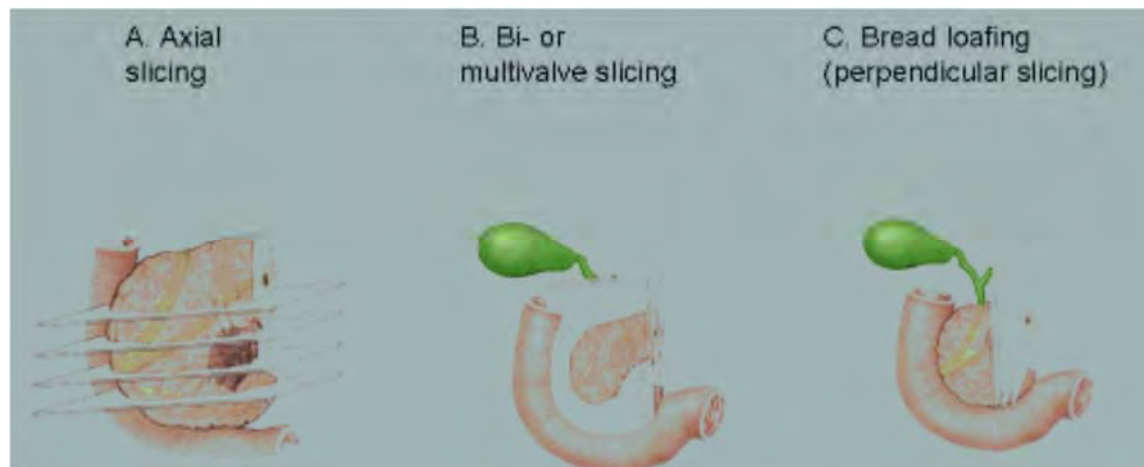


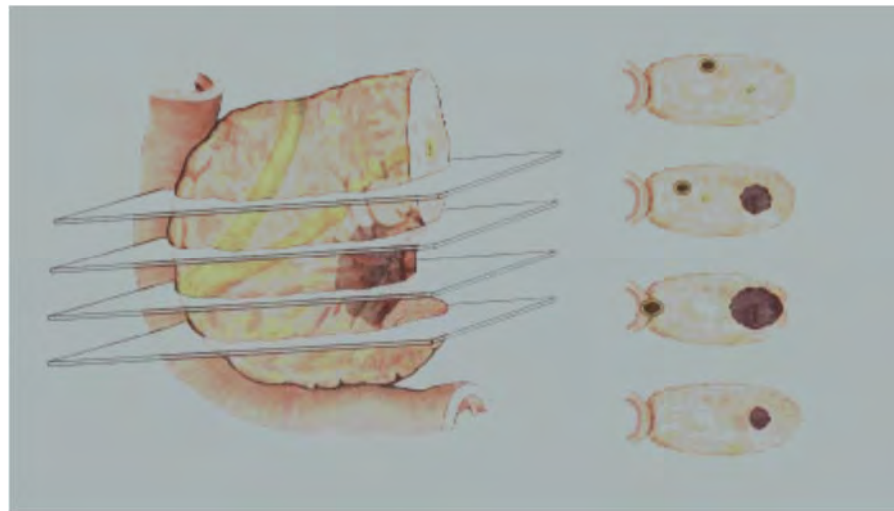
Image courtesy of Dr. N. Volkan Adsay

Figure 2. Whipple specimen with labeled margins.



Courtesy of Mr. Paul Brown, Specialist Medical Illustrator, St James's University Hospital Leeds

Figure 3. Slicing of pancreatoduodenectomy specimens.⁴⁵⁹



Courtesy of Mr. Paul Brown, Specialist Medical Illustrator, St James's University Hospital Leeds

Figure 4. Slicing of the pancreatoduodenectomy specimen in the axial plane to allow circumferential assessment of tumor.⁴⁵⁹

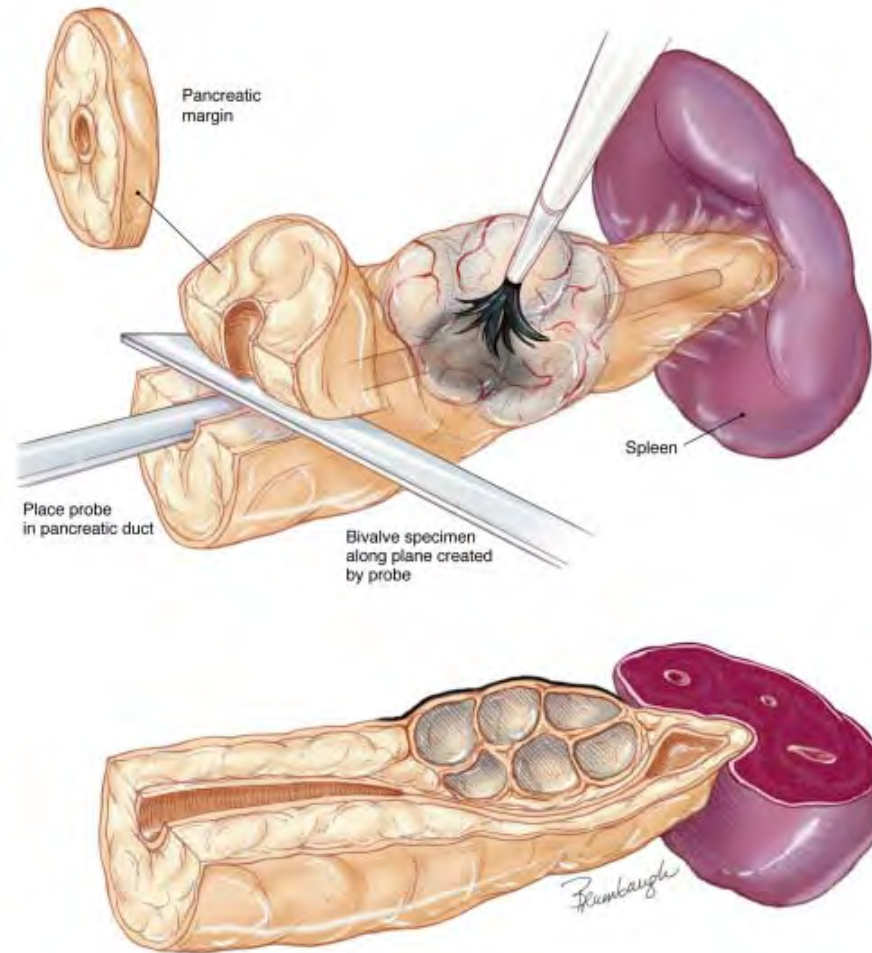


Figure 16-4, from Hruban, Ralph et al. Tumors of the Pancreas: Afip Atlas of Tumor Pathology, American Registry of Pathology, Washington DC 2007

Figure 5. Slicing of the distal pancreatectomy specimen.⁴⁷³

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9-29. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24399786>.
2. Arnold LD, Patel AV, Yan Y, et al. Are racial disparities in pancreatic cancer explained by smoking and overweight/obesity? Cancer Epidemiol Biomarkers Prev 2009;18:2397-2405. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19723915>.
3. Simard EP, Ward EM, Siegel R, Jemal A. Cancers with increasing incidence trends in the United States: 1999 through 2008. CA Cancer J Clin 2012. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22281605>.
4. Ehemann C, Henley SJ, Ballard-Barbash R, et al. Annual Report to the Nation on the status of cancer, 1975-2008, featuring cancers associated with excess weight and lack of sufficient physical activity. Cancer 2012;118:2338-2366. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22460733>.
5. Smith BD, Smith GL, Hurria A, et al. Future of cancer incidence in the United States: burdens upon an aging, changing nation. J Clin Oncol 2009;27:2758-2765. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19403886>.
6. StatBite. U.S. pancreatic cancer rates. J Natl Cancer Inst 2010;102:1822. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21139097>.
7. Worni M, Guller U, White RR, et al. Modest improvement in overall survival for patients with metastatic pancreatic cancer: a trend analysis using the surveillance, epidemiology, and end results registry from 1988 to 2008. Pancreas 2013;42:1157-1163. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23867367>.
8. Visser BC, Ma Y, Zak Y, et al. Failure to comply with NCCN guidelines for the management of pancreatic cancer compromises outcomes. HPB (Oxford) 2012;14:539-547. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22762402>.
9. Hoos WA, James PM, Rahib L, et al. Pancreatic cancer clinical trials and accrual in the United States. J Clin Oncol 2013;31:3432-3438. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23960185>.
10. U.S. National Library of Medicine-Key MEDLINE® Indicators. Available at: http://www.nlm.nih.gov/bsd/bsd_key.html. Accessed July 24, 2014.
11. Anderson MA, Zolotarevsky E, Cooper KL, et al. Alcohol and tobacco lower the age of presentation in sporadic pancreatic cancer in a dose-dependent manner: a multicenter study. Am J Gastroenterol 2012;107:1730-1739. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22929760>.
12. Bosetti C, Lucenteforte E, Silverman DT, et al. Cigarette smoking and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). Ann Oncol 2012;23:1880-1888. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22104574>.
13. Hassan MM, Bondy ML, Wolff RA, et al. Risk factors for pancreatic cancer: case-control study. Am J Gastroenterol 2007;102:2696-2707. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17764494>.
14. Lynch SM, Vrieling A, Lubin JH, et al. Cigarette smoking and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. Am J Epidemiol 2009;170:403-413. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19561064>.
15. Raimondi S, Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an overview. Nat Rev Gastroenterol Hepatol 2009;6:699-708. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19806144>.
16. Vrieling A, Bueno-de-Mesquita HB, Boshuizen HC, et al. Cigarette smoking, environmental tobacco smoke exposure and pancreatic



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cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2010;126:2394-2403. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19790196>.

17. Alsamarrai A, Das SL, Windsor JA, Petrov MS. Factors That Affect Risk for Pancreatic Disease in the General Population: A Systematic Review and Meta-analysis of Prospective Cohort Studies. *Clin Gastroenterol Hepatol* 2014;12:1635-1644 e1635. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24509242>.

18. Larsson SC, Orsini N, Wolk A. Body mass index and pancreatic cancer risk: A meta-analysis of prospective studies. *Int J Cancer* 2007;120:1993-1998. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17266034>.

19. Li D, Morris JS, Liu J, et al. Body mass index and risk, age of onset, and survival in patients with pancreatic cancer. *JAMA* 2009;301:2553-2562. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19549972>.

20. Patel AV, Rodriguez C, Bernstein L, et al. Obesity, recreational physical activity, and risk of pancreatic cancer in a large U.S. Cohort. *Cancer Epidemiol Biomarkers Prev* 2005;14:459-466. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15734973>.

21. Larsson SC, Wolk A. Red and processed meat consumption and risk of pancreatic cancer: meta-analysis of prospective studies. *Br J Cancer* 2012;106:603-607. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22240790>.

22. Thiebaut AC, Jiao L, Silverman DT, et al. Dietary fatty acids and pancreatic cancer in the NIH-AARP diet and health study. *J Natl Cancer Inst* 2009;101:1001-1011. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19561318>.

23. Genkinger JM, Wang M, Li R, et al. Dairy products and pancreatic cancer risk: a pooled analysis of 14 cohort studies. *Ann Oncol* 2014;25:1106-1115. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24631943>.

24. Rohrmann S, Linseisen J, Nothlings U, et al. Meat and fish consumption and risk of pancreatic cancer: results from the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2013;132:617-624. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22610753>.

25. Mancuso TF, el-Attar AA. Cohort study of workers exposed to betanaphthylamine and benzidine. *J Occup Med* 1967;9:277-285. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6026374>.

26. Lucenteforte E, La Vecchia C, Silverman D, et al. Alcohol consumption and pancreatic cancer: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). *Ann Oncol* 2012;23:374-382. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21536662>.

27. Wolpin BM, Ng K, Bao Y, et al. Plasma 25-hydroxyvitamin D and risk of pancreatic cancer. *Cancer Epidemiol Biomarkers Prev* 2012;21:82-91. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22086883>.

28. Duell EJ, Lucenteforte E, Olson SH, et al. Pancreatitis and pancreatic cancer risk: a pooled analysis in the International Pancreatic Cancer Case-Control Consortium (PanC4). *Ann Oncol* 2012;23:2964-2970. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22767586>.

29. Lowenfels AB, Maisonneuve P, Cavallini G, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. *N Engl J Med* 1993;328:1433-1437. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8479461>.

30. Malka D, Hammel P, Maire F, et al. Risk of pancreatic adenocarcinoma in chronic pancreatitis. *Gut* 2002;51:849-852. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12427788>.

31. Munigala S, Kanwal F, Xian H, et al. Increased risk of pancreatic adenocarcinoma after acute pancreatitis. *Clin Gastroenterol Hepatol*

2014;12:1143-1150 e1141. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/24440214>.

32. Bracci PM, Wang F, Hassan MM, et al. Pancreatitis and pancreatic cancer in two large pooled case-control studies. *Cancer Causes Control* 2009;20:1723-1731. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19760029>.

33. Chari ST, Leibson CL, Rabe KG, et al. Probability of pancreatic cancer following diabetes: a population-based study. *Gastroenterology* 2005;129:504-511. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16083707>.

34. Gullo L, Pezzilli R, Morselli-Labate AM. Diabetes and the risk of pancreatic cancer. Italian Pancreatic Cancer Study Group. *N Engl J Med* 1994;331:81-84. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/8208269>.

35. Gupta S, Vittinghoff E, Bertenthal D, et al. New-onset diabetes and pancreatic cancer. *Clin Gastroenterol Hepatol* 2006;4:1366-1372; quiz 1301. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16945591>.

36. Raghavan SR, Ballehaninna UK, Chamberlain RS. The impact of perioperative blood glucose levels on pancreatic cancer prognosis and surgical outcomes: an evidence-based review. *Pancreas* 2013;42:1210-1217. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24152946>.

37. Rosa JA, Van Linda BM, Abourizk NN. New-onset diabetes mellitus as a harbinger of pancreatic carcinoma. A case report and literature review. *J Clin Gastroenterol* 1989;11:211-215. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/2661661>.

38. Lee JH, Kim SA, Park HY, et al. New-onset diabetes patients need pancreatic cancer screening? *J Clin Gastroenterol* 2012;46:e58-61. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22138846>.

39. Sah RP, Nagpal SJ, Mukhopadhyay D, Chari ST. New insights into pancreatic cancer-induced paraneoplastic diabetes. *Nat Rev*

Gastroenterol Hepatol 2013;10:423-433. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23528347>.

40. Elena JW, Steplowski E, Yu K, et al. Diabetes and risk of pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. *Cancer Causes Control* 2013;24:13-25. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23112111>.

41. Pezzilli R, Casadei R, Morselli-Labate AM. Is type 2 diabetes a risk factor for pancreatic cancer? *JOP* 2009;10:705-706. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19890202>.

42. Bosetti C, Rosato V, Li D, et al. Diabetes, antidiabetic medications, and pancreatic cancer risk: an analysis from the International Pancreatic Cancer Case-Control Consortium. *Ann Oncol* 2014;25:2065-2072. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25057164>.

43. Bodmer M, Becker C, Meier C, et al. Use of antidiabetic agents and the risk of pancreatic cancer: a case-control analysis. *Am J Gastroenterol* 2012;107:620-626. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22290402>.

44. Li D, Yeung S-CJ, Hassan MM, et al. Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology* 2009;137:482-488. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19375425>.

45. Singh S, Singh PP, Singh AG, et al. Anti-diabetic medications and risk of pancreatic cancer in patients with diabetes mellitus: a systematic review and meta-analysis. *Am J Gastroenterol* 2013;108:510-519; quiz 520. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23399556>.

46. Franciosi M, Lucisano G, Lapice E, et al. Metformin therapy and risk of cancer in patients with type 2 diabetes: systematic review. *PLoS One* 2013;8:e71583. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23936520>.

47. Soranna D, Scotti L, Zambon A, et al. Cancer risk associated with use of metformin and sulfonylurea in type 2 diabetes: a meta-analysis.



NCCN Guidelines Version 2.2015 Pancreatic Adenocarcinoma

Oncologist 2012;17:813-822. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22643536>.

48. Wang Z, Lai ST, Xie L, et al. Metformin is associated with reduced risk of pancreatic cancer in patients with type 2 diabetes mellitus: A systematic review and meta-analysis. Diabetes Res Clin Pract 2014;106:19-26. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/24837144>.

49. Sadeghi N, Abbruzzese JL, Yeung SC, et al. Metformin use is associated with better survival of diabetic patients with pancreatic cancer. Clin Cancer Res 2012;18:2905-2912. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22465831>.

50. Toriola AT, Stolzenberg-Solomon R, Dalidowitz L, et al. Diabetes and pancreatic cancer survival: a prospective cohort-based study. Br J Cancer 2014;111:181-185. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/24786605>.

51. Hruban RH, Canto MI, Goggins M, et al. Update on familial pancreatic cancer. Adv Surg 2010;44:293-311. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/20919528>.

52. Humphris JL, Johns AL, Simpson SH, et al. Clinical and pathologic features of familial pancreatic cancer. Cancer 2014. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/25313458>.

53. Lynch HT, Smyrk T, Kern SE, et al. Familial pancreatic cancer: a review. Semin Oncol 1996;23:251-275. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/8623061>.

54. Wang W, Chen S, Brune KA, et al. PancPRO: risk assessment for individuals with a family history of pancreatic cancer. J Clin Oncol 2007;25:1417-1422. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17416862>.

55. Hemminki A, Markie D, Tomlinson I, et al. A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. Nature 1998;391:184-187. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9428765>.

56. Jenne DE, Reimann H, Nezu J, et al. Peutz-Jeghers syndrome is caused by mutations in a novel serine threonine kinase. Nat Genet 1998;18:38-43. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/9425897>.

57. Korsse SE, Harinck F, van Lier MG, et al. Pancreatic cancer risk in Peutz-Jeghers syndrome patients: a large cohort study and implications for surveillance. J Med Genet 2013;50:59-64. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23240097>.

58. Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology 2000;119:1447-1453. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/11113065>.

59. van Lier MG, Wagner A, Mathus-Vliegen EM, et al. High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. Am J Gastroenterol 2010;105:1258-1264; author reply 1265. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/20051941>.

60. Su GH, Hruban RH, Bansal RK, et al. Germline and somatic mutations of the STK11/LKB1 Peutz-Jeghers gene in pancreatic and biliary cancers. Am J Pathol 1999;154:1835-1840. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/10362809>.

61. Weiss FU. Pancreatic cancer risk in hereditary pancreatitis. Front Physiol 2014;5:70. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/24600409>.

62. LaRusch J, Solomon S, Whitcomb DC. Pancreatitis Overview. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. GeneReviews(R). Seattle (WA): University of Washington, Seattle; 2014.

63. Howes N, Lerch MM, Greenhalf W, et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe. Clin Gastroenterol Hepatol 2004;2:252-261. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15017610>.

64. Lowenfels AB, Maisonneuve P, DiMagno EP, et al. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Inst 1997;89:442-446. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9091646>.

65. Rebours V, Levy P, Ruzsiewicz P. An overview of hereditary pancreatitis. Dig Liver Dis 2012;44:8-15. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21907651>.

66. Whelan AJ, Bartsch D, Goodfellow PJ. Brief report: a familial syndrome of pancreatic cancer and melanoma with a mutation in the CDKN2 tumor-suppressor gene. N Engl J Med 1995;333:975-977. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7666917>.

67. de Snoo FA, Bishop DT, Bergman W, et al. Increased risk of cancer other than melanoma in CDKN2A founder mutation (p16-Leiden)-positive melanoma families. Clin Cancer Res 2008;14:7151-7157. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18981015>.

68. Vasen HF, Gruis NA, Frants RR, et al. Risk of developing pancreatic cancer in families with familial atypical multiple mole melanoma associated with a specific 19 deletion of p16 (p16-Leiden). Int J Cancer 2000;87:809-811. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10956390>.

69. Lynch HT, Brand RE, Hogg D, et al. Phenotypic variation in eight extended CDKN2A germline mutation familial atypical multiple mole melanoma-pancreatic carcinoma-prone families: the familial atypical mole melanoma-pancreatic carcinoma syndrome. Cancer 2002;94:84-96. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11815963>.

70. Ghiorzo P, Fornarini G, Sciallero S, et al. CDKN2A is the main susceptibility gene in Italian pancreatic cancer families. J Med Genet

2012;49:164-170. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22368299>.

71. Aaltonen LA, Salovaara R, Kristo P, et al. Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. N Engl J Med 1998;338:1481-1487. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9593786>.

72. Lindor NM, Petersen GM, Spurdle AB, et al. Pancreatic Cancer and a Novel MSH2 Germline Alteration. Pancreas 2011;40:1138-1140. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21926548>.

73. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. N Engl J Med 2003;348:919-932. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12621137>.

74. Hampel H, Frankel WL, Martin E, et al. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Med 2005;352:1851-1860. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15872200>.

75. Hampel H, Frankel WL, Martin E, et al. Feasibility of screening for Lynch syndrome among patients with colorectal cancer. J Clin Oncol 2008;26:5783-5788. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18809606>.

76. Boland CR, Goel A. Microsatellite instability in colorectal cancer. Gastroenterology 2010;138:2073-2087 e2073. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20420947>.

77. Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with Lynch syndrome. Jama 2009;302:1790-1795. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19861671>.

78. Win AK, Young JP, Lindor NM, et al. Colorectal and other cancer risks for carriers and noncarriers from families with a DNA mismatch repair gene mutation: a prospective cohort study. J Clin Oncol



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2012;30:958-964. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22331944>.

79. Cancer risks in BRCA2 mutation carriers. J Natl Cancer Inst 1999;91:1310-1316. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/10433620>.

80. Al-Sukhni W, Rothenmund H, Borgida AE, et al. Germline BRCA1 mutations predispose to pancreatic adenocarcinoma. Hum Genet 2008;124:271-278. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18762988>.

81. Ferrone CR, Levine DA, Tang LH, et al. BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. J Clin Oncol 2009;27:433-438. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19064968>.

82. Hahn SA, Greenhalf B, Ellis I, et al. BRCA2 germline mutations in familial pancreatic carcinoma. J Natl Cancer Inst 2003;95:214-221. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12569143>.

83. Iqbal J, Ragone A, Lubinski J, et al. The incidence of pancreatic cancer in BRCA1 and BRCA2 mutation carriers. Br J Cancer 2012;107:2005-2009. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23099806>.

84. van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, et al. Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med Genet 2005;42:711-719. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16141007>.

85. Liede A, Karlan BY, Narod SA. Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: a review of the literature. J Clin Oncol 2004;22:735-742. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/14966099>.

86. Couch FJ, Johnson MR, Rabe K, et al. Germ line Fanconi anemia complementation group C mutations and pancreatic cancer. Cancer

Res 2005;65:383-386. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/15695377>.

87. Slater EP, Langer P, Niemczyk E, et al. PALB2 mutations in European familial pancreatic cancer families. Clin Genet 2010;78:490-494. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20412113>.

88. van der Heijden MS, Yeo CJ, Hruban RH, Kern SE. Fanconi anemia gene mutations in young-onset pancreatic cancer. Cancer Res 2003;63:2585-2588. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/12750283>.

89. Roberts NJ, Jiao Y, Yu J, et al. ATM mutations in patients with hereditary pancreatic cancer. Cancer Discov 2012;2:41-46. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22585167>.

90. Klein AP, Brune KA, Petersen GM, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res 2004;64:2634-2638. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/15059921>.

91. Clores MJ, Thosani A, Buscaglia JM. Multidisciplinary diagnostic and therapeutic approaches to pancreatic cystic lesions. J Multidiscip Healthc 2014;7:81-91. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/24520195>.

92. Farrell JJ, Fernandez-del Castillo C. Pancreatic cystic neoplasms: management and unanswered questions. Gastroenterology 2013;144:1303-1315. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23622140>.

93. Law JK, Hruban RH, Lennon AM. Management of pancreatic cysts: a multidisciplinary approach. Curr Opin Gastroenterol 2013;29:509-516. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23872487>.

94. Tanaka M, Fernandez-del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of

the pancreas. *Pancreatology* 2012;12:183-197. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22687371>.

95. Del Chiaro M, Verbeke C, Salvia R, et al. European experts consensus statement on cystic tumours of the pancreas. *Dig Liver Dis* 2013;45:703-711. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23415799>.

96. Canto MI, Goggins M, Hruban RH, et al. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. *Clin Gastroenterol Hepatol* 2006;4:766-781; quiz 665. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16682259>.

97. Canto MI, Hruban RH, Fishman EK, et al. Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. *Gastroenterology* 2012;142:796-804; quiz e714-795. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22245846>.

98. Al-Sukhni W, Borgida A, Rothenmund H, et al. Screening for pancreatic cancer in a high-risk cohort: an eight-year experience. *J Gastrointest Surg* 2012;16:771-783. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22127781>.

99. Poley JW, Kluijdt I, Gouma DJ, et al. The yield of first-time endoscopic ultrasonography in screening individuals at a high risk of developing pancreatic cancer. *Am J Gastroenterol* 2009;104:2175-2181. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19491823>.

100. Langer P, Kann PH, Fendrich V, et al. Five years of prospective screening of high-risk individuals from families with familial pancreatic cancer. *Gut* 2009;58:1410-1418. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19470496>.

101. Ding Z, Wu H, Zhang J, et al. MicroRNAs as novel biomarkers for pancreatic cancer diagnosis: a meta-analysis based on 18 articles. *Tumour Biol* 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24880590>.

102. Kobayashi T, Nishiumi S, Ikeda A, et al. A novel serum metabolomics-based diagnostic approach to pancreatic cancer. *Cancer Epidemiol Biomarkers Prev* 2013;22:571-579. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23542803>.

103. Mayers JR, Wu C, Clish CB, et al. Elevation of circulating branched-chain amino acids is an early event in human pancreatic adenocarcinoma development. *Nat Med* 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25261994>.

104. Schultz NA, Dehlendorff C, Jensen BV, et al. MicroRNA biomarkers in whole blood for detection of pancreatic cancer. *Jama* 2014;311:392-404. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24449318>.

105. Liggett T, Melnikov A, Yi QL, et al. Differential methylation of cell-free circulating DNA among patients with pancreatic cancer versus chronic pancreatitis. *Cancer* 2010;116:1674-1680. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20143430>.

106. O'Brien DP, Sandanayake NS, Jenkinson C, et al. Serum CA19-9 is significantly up-regulated up to 2 years prior to diagnosis with pancreatic cancer: implications for early disease detection. *Clin Cancer Res* 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24938522>.

107. Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut* 2013;62:339-347. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23135763>.

108. Callery MP, Chang KJ, Fishman EK, et al. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. *Ann Surg Oncol* 2009;16:1727-1733. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19396496>.

109. Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of

the society of abdominal radiology and the american pancreatic association. *Gastroenterology* 2014;146:291-304.e291. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24355035>.

110. Edge SB, Byrd DR, Compton CC, et al., eds. *AJCC Cancer Staging Manual* (ed 7th). New York: Springer; 2010.

111. Bilimoria KY, Bentrem DJ, Ko CY, et al. Validation of the 6th edition AJCC Pancreatic Cancer Staging System: report from the National Cancer Database. *Cancer* 2007;110:738-744. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17580363>.

112. Wong JC, Lu DSK. Staging of pancreatic adenocarcinoma by imaging studies. *Clin Gastroenterol Hepatol* 2008;6:1301-1308. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18948228>.

113. Fuhrman GM, Charnsangavej C, Abbruzzese JL, et al. Thin-section contrast-enhanced computed tomography accurately predicts the resectability of malignant pancreatic neoplasms. *Am J Surg* 1994;167:104-111. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7906097>.

114. Horton KM, Fishman EK. Adenocarcinoma of the pancreas: CT imaging. *Radiol Clin North Am* 2002;40:1263-1272. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12479710>.

115. House MG, Yeo CJ, Cameron JL, et al. Predicting resectability of periaampullary cancer with three-dimensional computed tomography. *J Gastrointest Surg* 2004;8:280-288. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15019924>.

116. Klauss M, Schobinger M, Wolf I, et al. Value of three-dimensional reconstructions in pancreatic carcinoma using multidetector CT: initial results. *World J Gastroenterol* 2009;15:5827-5832. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19998504>.

117. McNulty NJ, Francis IR, Platt JF, et al. Multi-detector row helical CT of the pancreas: effect of contrast-enhanced multiphasic imaging on

enhancement of the pancreas, peripancreatic vasculature, and pancreatic adenocarcinoma. *Radiology* 2001;220:97-102. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11425979>.

118. Walters DM, Lapar DJ, de Lange EE, et al. Pancreas-protocol imaging at a high-volume center leads to improved preoperative staging of pancreatic ductal adenocarcinoma. *Ann Surg Oncol* 2011;18:2764-2771. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21484522>.

119. Schima W, Ba-Ssalamah A, Goetzinger P, et al. State-of-the-art magnetic resonance imaging of pancreatic cancer. *Top Magn Reson Imaging* 2007;18:421-429. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18303400>.

120. Vachiranubhap B, Kim YH, Balci NC, Semelka RC. Magnetic resonance imaging of adenocarcinoma of the pancreas. *Top Magn Reson Imaging* 2009;20:3-9. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19687720>.

121. Agarwal B, Abu-Hamda E, Molke KL, et al. Endoscopic ultrasound-guided fine needle aspiration and multidetector spiral CT in the diagnosis of pancreatic cancer. *Am J Gastroenterol* 2004;99:844-850. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15128348>.

122. Deerenberg EB, Poley JW, Hermans JJ, et al. Role of endoscopic ultrasonography in patients suspected of pancreatic cancer with negative helical MDCT scan. *Dig Surg* 2011;28:398-403. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22188923>.

123. Nawaz H, Fan CY, Kloke J, et al. Performance characteristics of endoscopic ultrasound in the staging of pancreatic cancer: a meta-analysis. *JOP* 2013;14:484-497. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24018593>.

124. Wang W, Shpaner A, Krishna SG, et al. Use of EUS-FNA in diagnosing pancreatic neoplasm without a definitive mass on CT. *Gastrointest Endosc* 2013;78:73-80. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23523302>.

125. Rosch T, Braig C, Gain T, et al. Staging of pancreatic and ampullary carcinoma by endoscopic ultrasonography. Comparison with conventional sonography, computed tomography, and angiography. *Gastroenterology* 1992;102:188-199. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1727753>.

126. Varadarajulu S, Wallace MB. Applications of endoscopic ultrasonography in pancreatic cancer. *Cancer Control* 2004;11:15-22. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14749619>.

127. Buchs NC, Chilcott M, Poletti PA, et al. Vascular invasion in pancreatic cancer: Imaging modalities, preoperative diagnosis and surgical management. *World J Gastroenterol* 2010;16:818-831. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20143460>.

128. Inoue K, Ohuchida J, Ohtsuka T, et al. Severe localized stenosis and marked dilatation of the main pancreatic duct are indicators of pancreatic cancer instead of chronic pancreatitis on endoscopic retrograde balloon pancreatography. *Gastrointest Endosc* 2003;58:510-515. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14520282>.

129. Nallamothu G, Hilden K, Adler DG. Endoscopic retrograde cholangiopancreatography for non-gastroenterologists: what you need to know. *Hosp Pract (Minneap)* 2011;39:70-80. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21576899>.

130. Pavey DA, Gress FG. The role of EUS-guided FNA for the evaluation of biliary strictures. *Gastrointest Endosc* 2006;64:334-337. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16923478>.

131. Tirkes T, Sandrasegaran K, Sanyal R, et al. Secretin-enhanced MR cholangiopancreatography: spectrum of findings. *Radiographics* 2013;33:1889-1906. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24224585>.

132. Farma JM, Santillan AA, Melis M, et al. PET/CT fusion scan enhances CT staging in patients with pancreatic neoplasms. *Ann Surg*

Oncol 2008;15:2465-2471. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18551347>.

133. Rijkers AP, Valkema R, Duivenvoorden HJ, van Eijck CH. Usefulness of F-18-fluorodeoxyglucose positron emission tomography to confirm suspected pancreatic cancer: a meta-analysis. *Eur J Surg Oncol* 2014;40:794-804. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24755095>.

134. Wang Z, Chen JQ, Liu JL, et al. FDG-PET in diagnosis, staging and prognosis of pancreatic carcinoma: a meta-analysis. *World J Gastroenterol* 2013;19:4808-4817. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23922481>.

135. Ahmed SI, Bochkarev V, Oleynikov D, Sasson AR. Patients with pancreatic adenocarcinoma benefit from staging laparoscopy. *J Laparoendosc Adv Surg Tech A* 2006;16:458-463. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17004868>.

136. Allen VB, Gurusamy KS, Takwoingi Y, et al. Diagnostic accuracy of laparoscopy following computed tomography (CT) scanning for assessing the resectability with curative intent in pancreatic and periampullary cancer. *Cochrane Database Syst Rev* 2013;11:Cd009323. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24272022>.

137. Warshaw AL, Gu ZY, Wittenberg J, Waltman AC. Preoperative staging and assessment of resectability of pancreatic cancer. *Arch Surg* 1990;125:230-233. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2154172>.

138. Andersson R, Vagianos CE, Williamson RCN. Preoperative staging and evaluation of resectability in pancreatic ductal adenocarcinoma. *HPB (Oxford)* 2004;6:5-12. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18333037>.

139. Alexakis N, Gomatos IP, Sbarounis S, et al. High serum CA 19-9 but not tumor size should select patients for staging laparoscopy in

radiological resectable pancreas head and peri-ampullary cancer. Eur J Surg Oncol 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25266999>.

140. Karachristos A, Scarneas N, Hoffman JP. CA 19-9 levels predict results of staging laparoscopy in pancreatic cancer. J Gastrointest Surg 2005;9:1286-1292. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16332484>.

141. White R, Winston C, Gonen M, et al. Current utility of staging laparoscopy for pancreatic and peripancreatic neoplasms. J Am Coll Surg 2008;206:445-450. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18308214>.

142. Ferrone CR, Haas B, Tang L, et al. The influence of positive peritoneal cytology on survival in patients with pancreatic adenocarcinoma. J Gastrointest Surg 2006;10:1347-1353. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17175453>.

143. Brugge WR, De Witt J, Klapman JB, et al. Techniques for cytologic sampling of pancreatic and bile duct lesions: The Papanicolaou Society of Cytopathology Guidelines. Cytojournal 2014;11:2. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25191516>.

144. Micames C, Jowell PS, White R, et al. Lower frequency of peritoneal carcinomatosis in patients with pancreatic cancer diagnosed by EUS-guided FNA vs. percutaneous FNA. Gastrointest Endosc 2003;58:690-695. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14595302>.

145. Okasha HH, Naga MI, Esmat S, et al. Endoscopic Ultrasound-Guided Fine Needle Aspiration versus Percutaneous Ultrasound-Guided Fine Needle Aspiration in Diagnosis of Focal Pancreatic Masses. Endosc Ultrasound 2013;2:190-193. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24949394>.

146. Layfield LJ, Dodd L, Factor R, Schmidt RL. Malignancy risk associated with diagnostic categories defined by the Papanicolaou

Society of Cytopathology pancreaticobiliary guidelines. Cancer Cytopathol 2014;122:420-427. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24339321>.

147. Chen YK, Pleskow DK. SpyGlass single-operator peroral cholangiopancreatography system for the diagnosis and therapy of bile-duct disorders: a clinical feasibility study (with video). Gastrointest Endosc 2007;65:832-841. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17466202>.

148. Strasberg SM, Middleton WD, Teefey SA, et al. Management of diagnostic dilemmas of the pancreas by ultrasonographically guided laparoscopic biopsy. Surgery 1999;126:736-741; discussion 741-733. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10520923>.

149. NIH state-of-the-science statement on endoscopic retrograde cholangiopancreatography (ERCP) for diagnosis and therapy. NIH Consens State Sci Statements 2002;19:1-26. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14768653>.

150. Campisi A, Brancatelli G, Vullierme MP, et al. Are pancreatic calcifications specific for the diagnosis of chronic pancreatitis? A multidetector-row CT analysis. Clin Radiol 2009;64:903-911. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19664481>.

151. Kajiwarra M, Kojima M, Konishi M, et al. Autoimmune pancreatitis with multifocal lesions. J Hepatobiliary Pancreat Surg 2008;15:449-452. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18670850>.

152. Kalady MF, Peterson B, Baillie J, et al. Pancreatic duct strictures: identifying risk of malignancy. Ann Surg Oncol 2004;11:581-588. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15150064>.

153. Menges M, Lerch MM, Zeitz M. The double duct sign in patients with malignant and benign pancreatic lesions. Gastrointest Endosc 2000;52:74-77. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10882966>.

154. Finkelberg DL, Sahani D, Deshpande V, Brugge WR. Autoimmune pancreatitis. *N Engl J Med* 2006;355:2670-2676. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17182992>.
155. Law R, Bronner M, Vogt D, Stevens T. Autoimmune pancreatitis: a mimic of pancreatic cancer. *Cleve Clin J Med* 2009;76:607-615. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19797461>.
156. Salla C, Chatzipantelis P, Konstantinou P, et al. EUS-FNA contribution in the identification of autoimmune pancreatitis: a case report. *JOP* 2007;8:598-604. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17873466>.
157. Holmes BJ, Hruban RH, Wolfgang CL, Ali SZ. Fine needle aspirate of autoimmune pancreatitis (lymphoplasmacytic sclerosing pancreatitis): cytomorphologic characteristics and clinical correlates. *Acta Cytol* 2012;56:228-232. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22555522>.
158. Learn PA, Grossman EB, Do RK, et al. Pitfalls in avoiding operation for autoimmune pancreatitis. *Surgery* 2011;150:968-974. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21893326>.
159. Hardacre JM, Iacobuzio-Donahue CA, Sohn TA, et al. Results of pancreaticoduodenectomy for lymphoplasmacytic sclerosing pancreatitis. *Ann Surg* 2003;237:853-858; discussion 858-859. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12796582>.
160. Sah RP, Chari ST. Autoimmune pancreatitis: an update on classification, diagnosis, natural history and management. *Curr Gastroenterol Rep* 2012;14:95-105. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22350841>.
161. Hamano H, Kawa S, Horiuchi A, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001;344:732-738. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11236777>.
162. van Heerde MJ, Buijs J, Hansen BE, et al. Serum level of Ca 19-9 increases ability of IgG4 test to distinguish patients with autoimmune pancreatitis from those with pancreatic carcinoma. *Dig Dis Sci* 2014;59:1322-1329. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24385012>.
163. Safi F, Roscher R, Bittner R, et al. High sensitivity and specificity of CA 19-9 for pancreatic carcinoma in comparison to chronic pancreatitis. Serological and immunohistochemical findings. *Pancreas* 1987;2:398-403. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3306667>.
164. Morris-Stiff G, Taylor MA. Ca19-9 and pancreatic cancer: Is it really that good? *J Gastrointest Oncol* 2012;3:88-89. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22811875>.
165. Ballehaninna UK, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence based appraisal. *J Gastrointest Oncol* 2012;3:105-119. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22811878>.
166. Hartwig W, Strobel O, Hinz U, et al. CA19-9 in potentially resectable pancreatic cancer: perspective to adjust surgical and perioperative therapy. *Ann Surg Oncol* 2013;20:2188-2196. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23247983>.
167. Kim YC, Kim HJ, Park JH, et al. Can preoperative CA19-9 and CEA levels predict the resectability of patients with pancreatic adenocarcinoma? *J Gastroenterol Hepatol* 2009;24:1869-1875. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19686409>.
168. Kondo N, Murakami Y, Uemura K, et al. Prognostic impact of perioperative serum CA 19-9 levels in patients with resectable pancreatic cancer. *Ann Surg Oncol* 2010;17:2321-2329. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20336387>.
169. Bauer TM, El-Rayes BF, Li X, et al. Carbohydrate antigen 19-9 is a prognostic and predictive biomarker in patients with advanced

pancreatic cancer who receive gemcitabine-containing chemotherapy: a pooled analysis of 6 prospective trials. *Cancer* 2013;119:285-292. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22786786>.

170. Berger AC, Garcia M, Hoffman JP, et al. Postresection CA 19-9 predicts overall survival in patients with pancreatic cancer treated with adjuvant chemoradiation: a prospective validation by RTOG 9704. *J Clin Oncol* 2008;26:5918-5922. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19029412>.

171. Berger AC, Winter K, Hoffman JP, et al. Five Year Results of US Intergroup/RTOG 9704 With Postoperative CA 19-9 $\leq$ 90 U/mL and Comparison to the CONKO-001 Trial. *Int J Radiat Oncol Biol Phys* 2012;84:e291-297. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22682806>.

172. Ferrone CR, Finkelstein DM, Thayer SP, et al. Perioperative CA19-9 levels can predict stage and survival in patients with resectable pancreatic adenocarcinoma. *J Clin Oncol* 2006;24:2897-2902. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16782929>.

173. Humphris JL, Chang DK, Johns AL, et al. The prognostic and predictive value of serum CA19.9 in pancreatic cancer. *Ann Oncol* 2012;23:1713-1722. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22241899>.

174. Montgomery RC, Hoffman JP, Riley LB, et al. Prediction of recurrence and survival by post-resection CA 19-9 values in patients with adenocarcinoma of the pancreas. *Ann Surg Oncol* 1997;4:551-556. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9367020>.

175. Tzeng CW, Balachandran A, Ahmad M, et al. Serum carbohydrate antigen 19-9 represents a marker of response to neoadjuvant therapy in patients with borderline resectable pancreatic cancer. *HPB (Oxford)* 2014;16:430-438. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23991810>.

176. Hess V, Glimelius B, Grawe P, et al. CA 19-9 tumour-marker response to chemotherapy in patients with advanced pancreatic cancer enrolled in a randomised controlled trial. *Lancet Oncol* 2008;9:132-138. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18249033>.

177. Pelzer U, Hilbig A, Sinn M, et al. Value of carbohydrate antigen 19-9 in predicting response and therapy control in patients with metastatic pancreatic cancer undergoing first-line therapy. *Front Oncol* 2013;3:155. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23785668>.

178. Halm U, Schumann T, Schiefke I, et al. Decrease of CA 19-9 during chemotherapy with gemcitabine predicts survival time in patients with advanced pancreatic cancer. *Br J Cancer* 2000;82:1013-1016. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10737382>.

179. Ishii H, Okada S, Sato T, et al. CA 19-9 in evaluating the response to chemotherapy in advanced pancreatic cancer. *Hepatogastroenterology* 1997;44:279-283. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9058159>.

180. Ko AH, Hwang J, Venook AP, et al. Serum CA19-9 response as a surrogate for clinical outcome in patients receiving fixed-dose rate gemcitabine for advanced pancreatic cancer. *Br J Cancer* 2005;93:195-199. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15999098>.

181. Wong D, Ko AH, Hwang J, et al. Serum CA19-9 decline compared to radiographic response as a surrogate for clinical outcomes in patients with metastatic pancreatic cancer receiving chemotherapy. *Pancreas* 2008;37:269-274. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18815548>.

182. Tempero MA, Uchida E, Takasaki H, et al. Relationship of carbohydrate antigen 19-9 and Lewis antigens in pancreatic cancer. *Cancer Res* 1987;47:5501-5503. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3308077>.

183. Mann DV, Edwards R, Ho S, et al. Elevated tumour marker CA19-9: clinical interpretation and influence of obstructive jaundice. *Eur J*



NCCN Guidelines Version 2.2015 Pancreatic Adenocarcinoma

Surg Oncol 2000;26:474-479. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/11016469>.

184. Marrelli D, Caruso S, Pedrazzani C, et al. CA19-9 serum levels in obstructive jaundice: clinical value in benign and malignant conditions. Am J Surg 2009;198:333-339. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19375064>.

185. Mackey JR, Mani RS, Selner M, et al. Functional nucleoside transporters are required for gemcitabine influx and manifestation of toxicity in cancer cell lines. Cancer Res 1998;58:4349-4357. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9766663>.

186. Farrell JJ, Elsaleh H, Garcia M, et al. Human equilibrative nucleoside transporter 1 levels predict response to gemcitabine in patients with pancreatic cancer. Gastroenterology 2009;136:187-195. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18992248>.

187. Greenhalf W, Ghaneh P, Neoptolemos JP, et al. Pancreatic cancer hENT1 expression and survival from gemcitabine in patients from the ESPAC-3 trial. J Natl Cancer Inst 2014;106:djt347. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24301456>.

188. Liu ZQ, Han YC, Zhang X, et al. Prognostic value of human equilibrative nucleoside transporter1 in pancreatic cancer receiving gemcitabine-based chemotherapy: a meta-analysis. PLoS One 2014;9:e87103. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/24475233>.

189. Marechal R, Bachet JB, Mackey JR, et al. Levels of gemcitabine transport and metabolism proteins predict survival times of patients treated with gemcitabine for pancreatic adenocarcinoma. Gastroenterology 2012;143:664-674 e661-666. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22705007>.

190. Saif M, Lee Y, Kim R. Harnessing gemcitabine metabolism: a step towards personalized medicine for pancreatic cancer. Ther Adv Med

Oncol 2012;4:341-346. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23118809>.

191. Zhu Y, Qi M, Lao L, et al. Human Equilibrative Nucleoside Transporter 1 Predicts Survival in Patients with Pancreatic Cancer Treated with Gemcitabine: A Meta-Analysis. Genet Test Mol Biomarkers 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24625353>.

192. Ormanns S, Heinemann V, Raponi M, et al. Human equilibrative nucleoside transporter 1 is not predictive for gemcitabine efficacy in advanced pancreatic cancer: translational results from the AIO-PK0104 phase III study with the clone SP120 rabbit antibody. Eur J Cancer 2014;50:1891-1899. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/24857044>.

193. Sinn M, Sinn BV, Stieler J, et al. Hent1 expression in patients with pancreatic cancer treated with gemcitabine after curative intended resection: Results from the CONKO-001 trial [abstract]. ASCO Meeting Abstracts 2014;32:4124. Available at:
http://meeting.ascopubs.org/cgi/content/abstract/32/15_suppl/4124.

194. Poplin E, Wasan H, Rolfe L, et al. Randomized, multicenter, phase II study of CO-101 versus gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma: including a prospective evaluation of the role of hENT1 in gemcitabine or CO-101 sensitivity. J Clin Oncol 2013;31:4453-4461. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/24220555>.

195. Burris HA, 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997;15:2403-2413. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/9196156>.

196. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA

2007;297:267-277. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17227978>.

197. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *JAMA* 2013;310:1473-1481. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24104372>.

198. Grunewald R, Abbruzzese JL, Tarassoff P, Plunkett W. Saturation of 2',2'-difluorodeoxycytidine 5'-triphosphate accumulation by mononuclear cells during a phase I trial of gemcitabine. *Cancer Chemother Pharmacol* 1991;27:258-262. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/1998982>.

199. Tempero M, Plunkett W, Ruiz Van Haperen V, et al. Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. *J Clin Oncol* 2003;21:3402-3408. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/12885837>.

200. Poplin E, Feng Y, Berlin J, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2009;27:3778-3785. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19581537>.

201. Demols A, Peeters M, Polus M, et al. Gemcitabine and oxaliplatin (GEMOX) in gemcitabine refractory advanced pancreatic adenocarcinoma: a phase II study. *Br J Cancer* 2006;94:481-485.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16434988>.

202. Fine RL, Fogelman DR, Schreiber SM, et al. The gemcitabine, docetaxel, and capecitabine (GTX) regimen for metastatic pancreatic cancer: a retrospective analysis. *Cancer Chemother Pharmacol* 2008;61:167-175. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17440727>.

203. Ko AH, Espinoza AM, Jones KA, et al. Optimizing the administration of fixed-dose rate gemcitabine plus capecitabine using an alternating-week schedule: a dose finding and early efficacy study in advanced pancreatic and biliary carcinomas. *Am J Clin Oncol* 2012;35:411-417. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21552099>.

204. Berlin JD, Catalano P, Thomas JP, et al. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. *J Clin Oncol* 2002;20:3270-3275.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12149301>.

205. Colucci G, Giuliani F, Gebbia V, et al. Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma: a prospective, randomized phase III study of the Gruppo Oncologia dell'Italia Meridionale. *Cancer* 2002;94:902-910. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11920457>.

206. Colucci G, Labianca R, Di Costanzo F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study. *J Clin Oncol* 2010;28:1645-1651. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20194854>.

207. Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol* 2009;27:5513-5518. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19858379>.

208. Heinemann V, Boeck S, Hinke A, et al. Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. *BMC Cancer* 2008;8:82-82. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18373843>.



NCCN Guidelines Version 2.2015 Pancreatic Adenocarcinoma

209. Heinemann V, Quietzsch D, Gieseler F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol* 2006;24:3946-3952. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16921047>.

210. Heinemann V, Labianca R, Hinke A, Louvet C. Increased survival using platinum analog combined with gemcitabine as compared to single-agent gemcitabine in advanced pancreatic cancer: pooled analysis of two randomized trials, the GERCOR/GISCAD intergroup study and a German multicenter study. *Ann Oncol* 2007;18:1652-1659. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17660491>.

211. Herrmann R, Bodoky G, Ruhstaller T, et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. *J Clin Oncol* 2007;25:2212-2217. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17538165>.

212. Louvet C, Labianca R, Hammel P, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol* 2005;23:3509-3516. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15908661>.

213. Reni M, Cordio S, Milandri C, et al. Gemcitabine versus cisplatin, epirubicin, fluorouracil, and gemcitabine in advanced pancreatic cancer: a randomised controlled multicentre phase III trial. *Lancet Oncol* 2005;6:369-376. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15925814>.

214. Rocha Lima CM, Green MR, Rotche R, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol* 2004;22:3776-3783. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15365074>.

215. Ciliberto D, Botta C, Correale P, et al. Role of gemcitabine-based combination therapy in the management of advanced pancreatic cancer: A meta-analysis of randomised trials. *Eur J Cancer* 2013;49:593-603. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22989511>.

216. Sun C, Ansari D, Andersson R, Wu DQ. Does gemcitabine-based combination therapy improve the prognosis of unresectable pancreatic cancer? *World J Gastroenterol* 2012;18:4944-4958. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23002368>.

217. Kulke MH, Tempero MA, Niedzwiecki D, et al. Randomized phase II study of gemcitabine administered at a fixed dose rate or in combination with cisplatin, docetaxel, or irinotecan in patients with metastatic pancreatic cancer: CALGB 89904. *J Clin Oncol* 2009;27:5506-5512. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19858396>.

218. Stathopoulos GP, Syrigos K, Aravantinos G, et al. A multicenter phase III trial comparing irinotecan-gemcitabine (IG) with gemcitabine (G) monotherapy as first-line treatment in patients with locally advanced or metastatic pancreatic cancer. *Br J Cancer* 2006;95:587-592. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16909140>.

219. Goncalves A, Gilabert M, Francois E, et al. BAYPAN study: a double-blind phase III randomized trial comparing gemcitabine plus sorafenib and gemcitabine plus placebo in patients with advanced pancreatic cancer. *Ann Oncol* 2012;23:2799-2805. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22771827>.

220. Von Hoff DD, Ramanathan RK, Borad MJ, et al. Gemcitabine Plus nab-Paclitaxel Is an Active Regimen in Patients With Advanced Pancreatic Cancer: A Phase I/II Trial. *J Clin Oncol* 2011;29:4548-4554. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21969517>.

221. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*

2013;369:1691-1703. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/24131140>.

222. Goldstein D, El-Maraghi RH, Hammel P, et al. Analyses of updated overall survival (OS) and prognostic effect of neutrophil-to-lymphocyte ratio (NLR) and CA 19-9 from the phase III MPACT study of nab-paclitaxel (nab-P) plus gemcitabine (Gem) versus Gem for patients (pts) with metastatic pancreatic cancer (PC) [abstract]. ASCO Meeting Abstracts 2014;32:4027. Available at:
http://meeting.ascopubs.org/cgi/content/abstract/32/15_suppl/4027.

223. Kindler HL, Friberg G, Singh DA, et al. Phase II trial of bevacizumab plus gemcitabine in patients with advanced pancreatic cancer. J Clin Oncol 2005;23:8033-8040. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16258101>.

224. Xiong HQ, Rosenberg A, LoBuglio A, et al. Cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor, in combination with gemcitabine for advanced pancreatic cancer: a multicenter phase II Trial. J Clin Oncol 2004;22:2610-2616. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/15226328>.

225. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007;25:1960-1966. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17452677>.

226. Philip PA, Benedetti J, Corless CL, et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. J Clin Oncol 2010;28:3605-3610. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20606093>.

227. Kindler HL, Niedzwiecki D, Hollis D, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia

Group B (CALGB 80303). J Clin Oncol 2010;28:3617-3622. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20606091>.

228. Kindler HL, Ioka T, Richel DJ, et al. Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase 3 study. Lancet Oncol 2011;12:256-262. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/21306953>.

229. Van Cutsem E, Vervenne WL, Bennouna J, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. J Clin Oncol 2009;27:2231-2237. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19307500>.

230. Rougier P, Riess H, Manges R, et al. Randomised, placebo-controlled, double-blind, parallel-group phase III study evaluating aflibercept in patients receiving first-line treatment with gemcitabine for metastatic pancreatic cancer. Eur J Cancer 2013;49:2633-2642. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23642329>.

231. Aranda E, Manzano JL, Rivera F, et al. Phase II open-label study of erlotinib in combination with gemcitabine in unresectable and/or metastatic adenocarcinoma of the pancreas: relationship between skin rash and survival (Pantar study). Ann Oncol 2012;23:1919-1925. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22156621>.

232. Stepanski EJ, Reyes C, Walker MS, et al. The association of rash severity with overall survival: findings from patients receiving erlotinib for pancreatic cancer in the community setting. Pancreas 2013;42:32-36. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22699203>.

233. Golan T, Kanji ZS, Epelbaum R, et al. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. Br J Cancer 2014;111:1132-1138. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/25072261>.

234. Majdak EJ, Debniak J, Milczek T, et al. Prognostic impact of BRCA1 pathogenic and BRCA1/BRCA2 unclassified variant mutations

in patients with ovarian carcinoma. Cancer 2005;104:1004-1012. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16047333>.

235. Stefansson OA, Jonasson JG, Johannsson OT, et al. Genomic profiling of breast tumours in relation to BRCA abnormalities and phenotypes. Breast Cancer Res 2009;11:R47. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19589159>.

236. Oliver GR, Sugar E, Laheru D, Diaz LA. Family history of cancer and sensitivity to platinum chemotherapy in pancreatic adenocarcinoma [abstract]. Gastrointestinal Cancers Symposium 2010:180. Available at: <http://meetinglibrary.asco.org/content/2395-72>.

237. Lowery MA, Kelsen DP, Stadler ZK, et al. An emerging entity: pancreatic adenocarcinoma associated with a known BRCA mutation: clinical descriptors, treatment implications, and future directions. Oncologist 2011;16:1397-1402. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21934105>.

238. Li Q, Yan H, Liu W, et al. Efficacy and safety of gemcitabine-fluorouracil combination therapy in the management of advanced pancreatic cancer: a meta-analysis of randomized controlled trials. PLoS One 2014;9:e104346. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25093849>.

239. De Jesus-Acosta A, Oliver GR, Blackford A, et al. A multicenter analysis of GTX chemotherapy in patients with locally advanced and metastatic pancreatic adenocarcinoma. Cancer Chemother Pharmacol 2012;69:415-424. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21800112>.

240. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 2004;350:1200-1210. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15028824>.

241. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following

pancreatic cancer resection: a randomized controlled trial. JAMA 2010;304:1073-1081. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20823433>.

242. Comparison of fluorouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. QUASAR Collaborative Group. Lancet 2000;355:1588-1596. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10821362>.

243. Jager E, Heike M, Bernhard H, et al. Weekly high-dose leucovorin versus low-dose leucovorin combined with fluorouracil in advanced colorectal cancer: results of a randomized multicenter trial. Study Group for Palliative Treatment of Metastatic Colorectal Cancer Study Protocol 1. J Clin Oncol 1996;14:2274-2279. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8708717>.

244. O'Connell MJ. A phase III trial of 5-fluorouracil and leucovorin in the treatment of advanced colorectal cancer. A Mayo Clinic/North Central Cancer Treatment Group study. Cancer 1989;63:1026-1030. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2465076>.

245. Ychou M, Conroy T, Seitz JF, et al. An open phase I study assessing the feasibility of the triple combination: oxaliplatin plus irinotecan plus leucovorin/ 5-fluorouracil every 2 weeks in patients with advanced solid tumors. Ann Oncol 2003;14:481-489. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12598357>.

246. Conroy T, Paillot B, Francois E, et al. Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer--a Groupe Tumeurs Digestives of the Federation Nationale des Centres de Lutte Contre le Cancer study. J Clin Oncol 2005;23:1228-1236. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15718320>.

247. Ychou M, Desseigne F, Guimbaud R, et al. Randomized phase II trial comparing folirinox (5FU/leucovorin [LV], irinotecan [I] and oxaliplatin [O]) vs gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma (MPA). First results of the ACCORD 11 trial [abstract]. J Clin Oncol 2007;25 (June 20 Suppl):4516. Available at:

http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/4516?sid=8904e4d6-689f-4715-8b08-891737076e04.

248. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817-1825. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21561347>.

249. Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. *J Clin Oncol* 2013;31:23-29. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23213101>.

250. Lowery MA, Yu KH, Adel NG, et al. Activity of front-line FOLFIRINOX (FFX) in stage III/IV pancreatic adenocarcinoma (PC) at Memorial Sloan-Kettering Cancer Center (MSKCC) [abstract]. *ASCO Meeting Abstracts* 2012;30:4057. Available at: http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/4057.

251. Boeck S, Vehling-Kaiser U, Waldschmidt D, et al. Erlotinib 150 mg daily plus chemotherapy in advanced pancreatic cancer: an interim safety analysis of a multicenter, randomized, cross-over phase III trial of the 'Arbeitsgemeinschaft Internistische Onkologie'. *Anticancer Drugs* 2010;21:94-100. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19770635>.

252. Cartwright TH, Cohn A, Varkey JA, et al. Phase II study of oral capecitabine in patients with advanced or metastatic pancreatic cancer. *J Clin Oncol* 2002;20:160-164. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11773165>.

253. Pelzer U, Schwaner I, Stieler J, et al. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. *Eur J Cancer* 2011;47:1676-1681. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21565490>.

254. Xiong HQ, Varadhachary GR, Blais JC, et al. Phase 2 trial of oxaliplatin plus capecitabine (XELOX) as second-line therapy for patients with advanced pancreatic cancer. *Cancer* 2008;113:2046-2052. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18756532>.

255. Reni M, Cereda S, Milella M, et al. Maintenance sunitinib or observation in metastatic pancreatic adenocarcinoma: a phase II randomised trial. *Eur J Cancer* 2013;49:3609-3615. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23899530>.

256. Rahma OE, Duffy A, Liewehr DJ, et al. Second-line treatment in advanced pancreatic cancer: a comprehensive analysis of published clinical trials. *Ann Oncol* 2013;24:1972-1979. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23670093>.

257. Maisey N, Chau I, Cunningham D, et al. Multicenter randomized phase III trial comparing protracted venous infusion (PVI) fluorouracil (5-FU) with PVI 5-FU plus mitomycin in inoperable pancreatic cancer. *J Clin Oncol* 2002;20:3130-3136. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12118027>.

258. Pelzer U, Kubica K, Stieler J, et al. A randomized trial in patients with gemcitabine refractory pancreatic cancer. Final results of the CONKO 003 study [abstract]. *J Clin Oncol* 2008;26 (May 20 suppl):4508. Available at: http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/4508?sid=31ed1378-2eda-4a39-8a2a-177afb2c9fb4.

259. Saif MW. New developments in the treatment of pancreatic cancer. Highlights from the "44th ASCO Annual Meeting". Chicago, IL, USA. May 30 - June 3, 2008. *JOP* 2008;9:391-397. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18648128>.

260. Oettle H, Riess H, Stieler JM, et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. *J Clin Oncol* 2014;32:2423-2429. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24982456>.

261. Gill S, Ko Y-J, Cripps MC, et al. PANCREOX: A randomized phase 3 study of 5FU/LV with or without oxaliplatin for second-line advanced pancreatic cancer (APC) in patients (pts) who have received gemcitabine (GEM)-based chemotherapy (CT) [abstract]. ASCO Meeting Abstracts 2014;32:4022. Available at: http://meeting.ascopubs.org/cgi/content/abstract/32/15_suppl/4022.

262. Heinemann V, Vehling-Kaiser U, Waldschmidt D, et al. Gemcitabine plus erlotinib followed by capecitabine versus capecitabine plus erlotinib followed by gemcitabine in advanced pancreatic cancer: final results of a randomised phase 3 trial of the 'Arbeitsgemeinschaft Internistische Onkologie' (AIO-PK0104). Gut 2013;62:751-759. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22773551>.

263. Seiwert TY, Salama JK, Vokes EE. The concurrent chemoradiation paradigm--general principles. Nat Clin Pract Oncol 2007;4:86-100. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17259930>.

264. Kalser MH, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. Arch Surg 1985;120:899-903. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/4015380>.

265. Moertel CG, Frytak S, Hahn RG, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. Cancer 1981;48:1705-1710. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7284971>.

266. Klinkenbijn JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and perampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg 1999;230:776-782. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10615932>.

267. Smeenk HG, van Eijck CHJ, Hop WC, et al. Long-term survival and metastatic pattern of pancreatic and periampullary cancer after

adjuvant chemoradiation or observation: long-term results of EORTC trial 40891. Ann Surg 2007;246:734-740. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17968163>.

268. Regine WF, Winter KA, Abrams RA, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. JAMA 2008;299:1019-1026. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18319412>.

269. Garofalo MC, Abrams RA, Regine WF. Adjuvant therapy for pancreatic cancer: no 'definite' standard. Oncology 2007;21:726-730. Available at: <http://www.cancernetwork.com/display/article/10165/61708>.

270. Regine WF, Winter KA, Abrams R, et al. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/RTOG 9704 phase III trial. Ann Surg Oncol 2011;18:1319-1326. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21499862>.

271. Crane CH, Ben-Josef E, Small W. Chemotherapy for pancreatic cancer. N Engl J Med 2004;350:2713-2715. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15218575>.

272. Koshy MC, Landry JC, Cavanaugh SX, et al. A challenge to the therapeutic nihilism of ESPAC-1. Int J Radiat Oncol Biol Phys 2005;61:965-966. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15752874>.

273. Morris SL, Beasley M, Leslie M. Chemotherapy for pancreatic cancer. N Engl J Med 2004;350:2713-2715; author reply 2713-2715. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15215490>.

274. Van Laethem JL, Hammel P, Mornex F, et al. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: a randomized EORTC-40013-

22012/FFCD-9203/GERCOR phase II study. J Clin Oncol 2010;28:4450-4456. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/20837948>.

275. Schmidt J, Abel U, Debus J, et al. Open-label, multicenter, randomized phase III trial of adjuvant chemoradiation plus interferon Alfa-2b versus fluorouracil and folinic acid for patients with resected pancreatic adenocarcinoma. J Clin Oncol 2012;30:4077-4083. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23008325>.

276. Ren F, Xu YC, Wang HX, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, for resectable advanced pancreatic adenocarcinoma: continue or stop? Pancreatolgy 2012;12:162-169. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22487527>.

277. Liao WC, Chien KL, Lin YL, et al. Adjuvant treatments for resected pancreatic adenocarcinoma: a systematic review and network meta-analysis. Lancet Oncol 2013;14:1095-1103. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24035532>.

278. Kooby DA, Gillespie TW, Liu Y, et al. Impact of adjuvant radiotherapy on survival after pancreatic cancer resection: an appraisal of data from the national cancer data base. Ann Surg Oncol 2013;20:3634-3642. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23771249>.

279. Morganti AG, Falconi M, van Stiphout RG, et al. Multi-institutional Pooled Analysis on Adjuvant Chemoradiation in Pancreatic Cancer. Int J Radiat Oncol Biol Phys 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25220717>.

280. Neoptolemos JP, Stocken DD, Dunn JA, et al. Influence of resection margins on survival for patients with pancreatic cancer treated by adjuvant chemoradiation and/or chemotherapy in the ESPAC-1 randomized controlled trial. Ann Surg 2001;234:758-768. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11729382>.

281. Herman JM, Swartz MJ, Hsu CC, et al. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: results of a large, prospectively collected database at the Johns Hopkins Hospital. J Clin Oncol 2008;26:3503-3510. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18640931>.

282. Corsini MM, Miller RC, Haddock MG, et al. Adjuvant radiotherapy and chemotherapy for pancreatic carcinoma: the Mayo Clinic experience (1975-2005). J Clin Oncol 2008;26:3511-3516. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18640932>.

283. Hsu CC, Herman JM, Corsini MM, et al. Adjuvant chemoradiation for pancreatic adenocarcinoma: the Johns Hopkins Hospital-Mayo Clinic collaborative study. Ann Surg Oncol 2010;17:981-990. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20087786>.

284. Butturini G, Stocken DD, Wente MN, et al. Influence of resection margins and treatment on survival in patients with pancreatic cancer: meta-analysis of randomized controlled trials. Arch Surg 2008;143:75-83; discussion 83. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18209156>.

285. Redmond KJ, Wolfgang CL, Sugar EA, et al. Adjuvant chemoradiation therapy for adenocarcinoma of the distal pancreas. Ann Surg Oncol 2010;17:3112-3119. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20680697>.

286. Stocken DD, Buchler MW, Dervenis C, et al. Meta-analysis of randomised adjuvant therapy trials for pancreatic cancer. Br J Cancer 2005;92:1372-1381. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15812554>.

287. Kim R, Saif MW. Is there an optimal neoadjuvant therapy for locally advanced pancreatic cancer? JOP 2007;8:279-288. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17495356>.

288. Crane CH, Abbruzzese JL, Evans DB, et al. Is the therapeutic index better with gemcitabine-based chemoradiation than with 5-fluorouracil-based chemoradiation in locally advanced pancreatic cancer? *Int J Radiat Oncol Biol Phys* 2002;52:1293-1302. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11955742>.

289. Blackstock AW, Tepper JE, Niedwiecki D, et al. Cancer and leukemia group B (CALGB) 89805: phase II chemoradiation trial using gemcitabine in patients with locoregional adenocarcinoma of the pancreas. *Int J Gastrointest Cancer* 2003;34:107-116. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15361643>.

290. Girard N, Mornex F, Bossard N, et al. Estimating optimal dose of twice-weekly gemcitabine for concurrent chemoradiotherapy in unresectable pancreatic carcinoma: mature results of GEMRT-01 Phase I trial. *Int J Radiat Oncol Biol Phys* 2010;77:1426-1432. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20056351>.

291. Loehrer PJ, Powell ME, Cardenes HR, et al. A randomized phase III study of gemcitabine in combination with radiation therapy versus gemcitabine alone in patients with localized, unresectable pancreatic cancer: E4201 [abstract]. *J Clin Oncol* 2008;26 (May 20 suppl):4506. Available at: http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/4506?sid=526086db-bb84-4435-b063-52f14bdacd3c.

292. Murphy JD, Adusumilli S, Griffith KA, et al. Full-dose gemcitabine and concurrent radiotherapy for unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2007;68:801-808. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17379445>.

293. Shibuya K, Oya N, Fujii T, et al. Phase II Study of Radiation Therapy Combined With Weekly Low-Dose Gemcitabine for Locally Advanced, Unresectable Pancreatic Cancer. *Am J Clin Oncol* 2010;34:115-119. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20065850>.

294. Huang J, Robertson JM, Margolis J, et al. Long-term results of full-dose gemcitabine with radiation therapy compared to 5-fluorouracil with radiation therapy for locally advanced pancreas cancer. *Radiother Oncol* 2011;99:114-119. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21621866>.

295. Zhu CP, Shi J, Chen YX, et al. Gemcitabine in the chemoradiotherapy for locally advanced pancreatic cancer: a meta-analysis. *Radiother Oncol* 2011;99:108-113. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21571383>.

296. Mukherjee S, Hurt CN, Bridgewater J, et al. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. *Lancet Oncol* 2013;14:317-326. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23474363>.

297. Chen Y, Sun XJ, Jiang TH, Mao AW. Combined radiochemotherapy in patients with locally advanced pancreatic cancer: a meta-analysis. *World J Gastroenterol* 2013;19:7461-7471. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24259979>.

298. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. Gastrointestinal Tumor Study Group. *J Natl Cancer Inst* 1988;80:751-755. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2898536>.

299. Klaassen DJ, MacIntyre JM, Catton GE, et al. Treatment of locally unresectable cancer of the stomach and pancreas: a randomized comparison of 5-fluorouracil alone with radiation plus concurrent and maintenance 5-fluorouracil--an Eastern Cooperative Oncology Group study. *J Clin Oncol* 1985;3:373-378. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3973648>.

300. Brunner TB, Grabenbauer GG, Kastl S, et al. Preoperative Chemoradiation in Locally Advanced Pancreatic Carcinoma: A Phase II

Study. *Onkologie* 2000;23:436-442. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/11441238>.

301. Macchia G, Valentini V, Mattiucci GC, et al. Preoperative chemoradiation and intra-operative radiotherapy for pancreatic carcinoma. *Tumori* 2007;93:53-60. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17455872>.

302. Thomas CR, Jr., Weiden PL, Traverso LW, Thompson T. Concomitant intraarterial cisplatin, intravenous 5-fluorouracil, and split-course radiation therapy for locally advanced unresectable pancreatic adenocarcinoma: a phase II study of the Puget Sound Oncology Consortium (PSOC-703). *Am J Clin Oncol* 1997;20:161-165. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9124192>.

303. Cinar P, Ko AH. Evolving treatment options for locally advanced unresectable pancreatic ductal adenocarcinoma. *J Natl Compr Canc Netw* 2014;12:167-172. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/24586078>.

304. Loehrer PJ, Sr., Feng Y, Cardenes H, et al. Gemcitabine Alone Versus Gemcitabine Plus Radiotherapy in Patients With Locally Advanced Pancreatic Cancer: An Eastern Cooperative Oncology Group Trial. *J Clin Oncol* 2011;29:4105-4112. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/21969502>.

305. Philip PA. Locally Advanced Pancreatic Cancer: Where Should We Go From Here? *J Clin Oncol* 2011;29:4066-4068. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/21969514>.

306. Chauffert B, Mornex F, Bonnetain F, et al. Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. *Ann Oncol* 2008;19:1592-1599. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18467316>.

307. Huguet F, Andre T, Hammel P, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J Clin Oncol* 2007;25:326-331. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17235048>.

308. Huguet F, Girard N, Guerche CS-E, et al. Chemoradiotherapy in the management of locally advanced pancreatic carcinoma: a qualitative systematic review. *J Clin Oncol* 2009;27:2269-2277. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19307501>.

309. Krishnan S, Rana V, Janjan NA, et al. Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. *Cancer* 2007;110:47-55. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17538975>.

310. Hammel P, Huguet F, Van Laethem J-L, et al. Comparison of chemoradiotherapy (CRT) and chemotherapy (CT) in patients with a locally advanced pancreatic cancer (LAPC) controlled after 4 months of gemcitabine with or without erlotinib: Final results of the international phase III LAP 07 study [abstract]. *ASCO Meeting Abstracts* 2013;31:LBA4003. Available at:
http://meeting.ascopubs.org/cgi/content/abstract/31/18_suppl/LBA4003.

311. Huguet F, Hammel P, Vernerey D, et al. Impact of chemoradiotherapy (CRT) on local control and time without treatment in patients with locally advanced pancreatic cancer (LAPC) included in the international phase III LAP 07 study [abstract]. *ASCO Meeting Abstracts* 2014;32:4001. Available at:
http://meeting.ascopubs.org/cgi/content/abstract/32/15_suppl/4001.

312. Bai YR, Wu GH, Guo WJ, et al. Intensity modulated radiation therapy and chemotherapy for locally advanced pancreatic cancer: results of feasibility study. *World J Gastroenterol* 2003;9:2561-2564. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14606097>.

313. Combs SE, Habermehl D, Kessel K, et al. Intensity modulated radiotherapy as neoadjuvant chemoradiation for the treatment of patients with locally advanced pancreatic cancer. Outcome analysis and comparison with a 3D-treated patient cohort. *Strahlenther Onkol* 2013;189:738-744. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23896630>.

314. Crane CH, Antolak JA, Rosen, II, et al. Phase I study of concomitant gemcitabine and IMRT for patients with unresectable adenocarcinoma of the pancreatic head. *Int J Gastrointest Cancer* 2001;30:123-132. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/12540024>.

315. Milano MT, Chmura SJ, Garofalo MC, et al. Intensity-modulated radiotherapy in treatment of pancreatic and bile duct malignancies: toxicity and clinical outcome. *Int J Radiat Oncol Biol Phys* 2004;59:445-453. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15145161>.

316. Spalding AC, Jee K-W, Vineberg K, et al. Potential for dose-escalation and reduction of risk in pancreatic cancer using IMRT optimization with lexicographic ordering and gEUD-based cost functions. *Med Phys* 2007;34:521-529. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17388169>.

317. Yovino S, Poppe M, Jabbour S, et al. Intensity-modulated radiation therapy significantly improves acute gastrointestinal toxicity in pancreatic and ampullary cancers. *Int J Radiat Oncol Biol Phys* 2011;79:158-162. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20399035>.

318. Chang DT, Schellenberg D, Shen J, et al. Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. *Cancer* 2009;115:665-672. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19117351>.

319. Chuong MD, Springett GM, Freilich JM, et al. Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated. *Int J Radiat Oncol Biol*

Phys 2013;86:516-522. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23562768>.

320. Herman JM, Koong AC. Stereotactic body radiation therapy: a new standard option for pancreatic cancer? *J Natl Compr Canc Netw* 2014;12:1489-1493. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25313185>.

321. Rwigema JC, Parikh SD, Heron DE, et al. Stereotactic body radiotherapy in the treatment of advanced adenocarcinoma of the pancreas. *Am J Clin Oncol* 2011;34:63-69. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20308870>.

322. Tozzi A, Comito T, Alongi F, et al. SBRT in unresectable advanced pancreatic cancer: preliminary results of a mono-institutional experience. *Radiat Oncol* 2013;8:148. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23799996>.

323. Wild AT, Hiniker SM, Chang DT, et al. Re-irradiation with stereotactic body radiation therapy as a novel treatment option for isolated local recurrence of pancreatic cancer after multimodality therapy: experience from two institutions. *J Gastrointest Oncol* 2013;4:343-351. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24294505>.

324. Gunderson LL, Martin JK, Kvols LK, et al. Intraoperative and external beam irradiation +/- 5-FU for locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 1987;13:319-329. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/3104244>.

325. Gunderson LL, Martin JK, Jr., Earle JD, et al. Intraoperative and external beam irradiation with or without resection: Mayo pilot experience. *Mayo Clin Proc* 1984;59:691-699. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/6482514>.

326. Mohiuddin M, Regine WF, Stevens J, et al. Combined intraoperative radiation and perioperative chemotherapy for

unresectable cancers of the pancreas. J Clin Oncol 1995;13:2764-2768. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7595736>.

327. Roldan GE, Gunderson LL, Nagorney DM, et al. External beam versus intraoperative and external beam irradiation for locally advanced pancreatic cancer. Cancer 1988;61:1110-1116. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3342371>.

328. Ashman JB, Moss AA, Rule WG, et al. Preoperative chemoradiation and IOERT for unresectable or borderline resectable pancreas cancer. J Gastrointest Oncol 2013;4:352-360. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24294506>.

329. Cai S, Hong TS, Goldberg SI, et al. Updated long-term outcomes and prognostic factors for patients with unresectable locally advanced pancreatic cancer treated with intraoperative radiotherapy at the Massachusetts General Hospital, 1978 to 2010. Cancer 2013;119:4196-4204. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24006012>.

330. Jingu K, Tanabe T, Nemoto K, et al. Intraoperative radiotherapy for pancreatic cancer: 30-year experience in a single institution in Japan. Int J Radiat Oncol Biol Phys 2012;83:e507-511. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22445002>.

331. Palta M, Willett C, Czito B. The role of intraoperative radiation therapy in patients with pancreatic cancer. Semin Radiat Oncol 2014;24:126-131. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24635869>.

332. Faris JE, Blaszkowsky LS, McDermott S, et al. FOLFIRINOX in locally advanced pancreatic cancer: the Massachusetts General Hospital Cancer Center experience. Oncologist 2013;18:543-548. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23657686>.

333. Ammori JB, Colletti LM, Zalupski MM, et al. Surgical resection following radiation therapy with concurrent gemcitabine in patients with previously unresectable adenocarcinoma of the pancreas. J

Gastrointest Surg 2003;7:766-772. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/13129554>.

334. Bickenbach KA, Gonen M, Tang LH, et al. Downstaging in pancreatic cancer: a matched analysis of patients resected following systemic treatment of initially locally unresectable disease. Ann Surg Oncol 2012;19:1663-1669. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22130621>.

335. Habermehl D, Kessel K, Welzel T, et al. Neoadjuvant chemoradiation with Gemcitabine for locally advanced pancreatic cancer. Radiat Oncol 2012;7:28. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22385572>.

336. Kadera BE, Sunjaya DB, Isacoff WH, et al. Locally advanced pancreatic cancer: association between prolonged preoperative treatment and lymph-node negativity and overall survival. JAMA Surg 2014;149:145-153. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24306217>.

337. Massucco P, Capussotti L, Magnino A, et al. Pancreatic resections after chemoradiotherapy for locally advanced ductal adenocarcinoma: analysis of perioperative outcome and survival. Ann Surg Oncol 2006;13:1201-1208. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16955382>.

338. Mondo EL, Noel MS, Katz AW, et al. Unresectable locally advanced pancreatic cancer: treatment with neoadjuvant leucovorin, fluorouracil, irinotecan, and oxaliplatin and assessment of surgical resectability. J Clin Oncol 2013;31:e37-39. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23233707>.

339. Mornex F, Girard N, Delperio J-R, Partensky C. Radiochemotherapy in the management of pancreatic cancer--part I: neoadjuvant treatment. Semin Radiat Oncol 2005;15:226-234. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16183476>.

340. Quiros RM, Brown KM, Hoffman JP. Neoadjuvant therapy in pancreatic cancer. *Cancer Invest* 2007;25:267-273. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17612937>.

341. White RR, Hurwitz HI, Morse MA, et al. Neoadjuvant chemoradiation for localized adenocarcinoma of the pancreas. *Ann Surg Oncol* 2001;8:758-765. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11776488>.

342. Gillen S, Schuster T, Meyer Zum Buschenfelde C, et al. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med* 2010;7:e1000267. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20422030>.

343. Li D, Xie K, Wolff R, Abbruzzese JL. Pancreatic cancer. *Lancet* 2004;363:1049-1057. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15051286>.

344. Gudjonsson B. Cancer of the pancreas. 50 years of surgery. *Cancer* 1987;60:2284-2303. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3326653>.

345. Crist DW, Sitzmann JV, Cameron JL. Improved hospital morbidity, mortality, and survival after the Whipple procedure. *Ann Surg* 1987;206:358-365. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3632096>.

346. Allison DC, Piantadosi S, Hruban RH, et al. DNA content and other factors associated with ten-year survival after resection of pancreatic carcinoma. *J Surg Oncol* 1998;67:151-159. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9530884>.

347. Howard TJ, Krug JE, Yu J, et al. A margin-negative R0 resection accomplished with minimal postoperative complications is the surgeon's contribution to long-term survival in pancreatic cancer. *J Gastrointest Surg* 2006;10:1338-1345. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17175452>.

348. Sohn TA, Yeo CJ, Cameron JL, et al. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg* 2000;4:567-579. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11307091>.

349. Bilimoria KY, Talamonti MS, Sener SF, et al. Effect of hospital volume on margin status after pancreaticoduodenectomy for cancer. *J Am Coll Surg* 2008;207:510-519. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18926452>.

350. Winter JM, Cameron JL, Campbell KA, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: A single-institution experience. *J Gastrointest Surg* 2006;10:1199-1210; discussion 1210-1191. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17114007>.

351. Zervos EE, Rosemurgy AS, Al-Saif O, Durkin AJ. Surgical management of early-stage pancreatic cancer. *Cancer Control* 2004;11:23-31. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14749620>.

352. Abrams RA, Lowy AM, O'Reilly EM, et al. Combined modality treatment of resectable and borderline resectable pancreas cancer: expert consensus statement. *Ann Surg Oncol* 2009;16:1751-1756. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19390900>.

353. Bockhorn M, Uzunoglu FG, Adham M, et al. Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 2014;155:977-988. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24856119>.

354. Sobin LH, Gospodarowicz MK, Wittekind C, eds. *TNM Classification of Malignant Tumours* (ed 7th): John Wiley & Sons; 2009.

355. Varadhachary GR, Tamm EP, Abbruzzese JL, et al. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. *Ann Surg Oncol* 2006;13:1035-1046. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16865597>.

356. Katz MH, Marsh R, Herman JM, et al. Borderline resectable pancreatic cancer: need for standardization and methods for optimal clinical trial design. *Ann Surg Oncol* 2013;20:2787-2795. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23435609>.

357. Talamonti M. Borderline resectable pancreatic cancer: a new classification for an old challenge. *Ann Surg Oncol* 2006;13:1019-1020. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16865593>.

358. Gumbs AA, Rodriguez Rivera AM, Milone L, Hoffman JP. Laparoscopic Pancreatoduodenectomy: A Review of 285 Published Cases. *Ann Surg Oncol* 2011;18:1335-1341. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21207166>.

359. Venkat R, Edil BH, Schulick RD, et al. Laparoscopic distal pancreatectomy is associated with significantly less overall morbidity compared to the open technique: a systematic review and meta-analysis. *Ann Surg* 2012;255:1048-1059. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22511003>.

360. Nakeeb A, Lillemoe KD, Grosfeld JL. Surgical techniques for pancreatic cancer. *Minerva Chir* 2004;59:151-163. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15238889>.

361. Yeo TP, Hruban RH, Leach SD, et al. Pancreatic cancer. *Curr Probl Cancer* 2002;26:176-275. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12399802>.

362. Baque P, Iannelli A, Delotte J, et al. Division of the right posterior attachments of the head of the pancreas with a linear stapler during pancreaticoduodenectomy: vascular and oncological considerations based on an anatomical cadaver-based study. *Surg Radiol Anat* 2009;31:13-17. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18712270>.

363. Evans DB, Pisters PW. Novel applications of endo GIA linear staplers during pancreaticoduodenectomy and total pancreatectomy.

Am J Surg 2003;185:606-607. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12781900>.

364. Harrison LE, Klimstra DS, Brennan MF. Isolated portal vein involvement in pancreatic adenocarcinoma. A contraindication for resection? *Ann Surg* 1996;224:342-347; discussion 347-349. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8813262>.

365. Riediger H, Makowiec F, Fischer E, et al. Postoperative morbidity and long-term survival after pancreaticoduodenectomy with superior mesenterico-portal vein resection. *J Gastrointest Surg* 2006;10:1106-1115. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16966029>.

366. Tseng JF, Raut CP, Lee JE, et al. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. *J Gastrointest Surg* 2004;8:935-949. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15585381>.

367. Stitzenberg KB, Watson JC, Roberts A, et al. Survival after pancreatectomy with major arterial resection and reconstruction. *Ann Surg Oncol* 2008;15:1399-1406. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18320285>.

368. Mollberg N, Rahbari NN, Koch M, et al. Arterial resection during pancreatectomy for pancreatic cancer: a systematic review and meta-analysis. *Ann Surg* 2011;254:882-893. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22064622>.

369. Worni M, Castleberry AW, Clary BM, et al. Concomitant Vascular Reconstruction During Pancreatectomy for Malignant Disease: A Propensity Score-Adjusted, Population-Based Trend Analysis Involving 10 206 Patients. *Arch Surg* 2012;1-8. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23247767>.

370. Christein JD, Kendrick ML, Iqbal CW, et al. Distal pancreatectomy for resectable adenocarcinoma of the body and tail of the pancreas. *J Gastrointest Surg* 2005;9:922-927. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16137585>.

371. Shoup M, Conlon KC, Klimstra D, Brennan MF. Is extended resection for adenocarcinoma of the body or tail of the pancreas justified? J Gastrointest Surg 2003;7:946-952; discussion 952. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14675703>.

372. Strasberg SM, Linehan DC, Hawkins WG. Radical antegrade modular pancreateosplenectomy procedure for adenocarcinoma of the body and tail of the pancreas: ability to obtain negative tangential margins. J Am Coll Surg 2007;204:244-249. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17254928>.

373. Stauffer JA, Rosales-Velderrain A, Goldberg RF, et al. Comparison of open with laparoscopic distal pancreatectomy: a single institution's transition over a 7-year period. HPB (Oxford) 2013;15:149-155. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23297726>.

374. Pericleous S, Middleton N, McKay SC, et al. Systematic review and meta-analysis of case-matched studies comparing open and laparoscopic distal pancreatectomy: is it a safe procedure? Pancreas 2012;41:993-1000. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22836858>.

375. Tran Cao HS, Lopez N, Chang DC, et al. Improved perioperative outcomes with minimally invasive distal pancreatectomy: results from a population-based analysis. JAMA Surg 2014;149:237-243. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24402232>.

376. Fortner JG. Regional pancreatectomy for cancer of the pancreas, ampulla, and other related sites. Tumor staging and results. Ann Surg 1984;199:418-425. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6712317>.

377. Fuhrman GM, Leach SD, Staley CA, et al. Rationale for en bloc vein resection in the treatment of pancreatic adenocarcinoma adherent to the superior mesenteric-portal vein confluence. Pancreatic Tumor Study Group. Ann Surg 1996;223:154-162. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8597509>.

378. Leach SD, Lee JE, Charnsangavej C, et al. Survival following pancreaticoduodenectomy with resection of the superior mesenteric-portal vein confluence for adenocarcinoma of the pancreatic head. Br J Surg 1998;85:611-617. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9635805>.

379. Clavien PA, Rudiger HA. A simple technique of portal vein resection and reconstruction during pancreaticoduodenectomy. J Am Coll Surg 1999;189:629-634. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10589601>.

380. Launois B, Stasik C, Bardaxoglou E, et al. Who benefits from portal vein resection during pancreaticoduodenectomy for pancreatic cancer? World J Surg 1999;23:926-929. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10449822>.

381. Taschieri AM, Elli M, Rovati M, et al. Surgical treatment of pancreatic tumors invading the spleno-mesenteric-portal vessels. An Italian Multicenter Survey. Hepatogastroenterology 1999;46:492-497. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10228849>.

382. van Geenen RC, ten Kate FJ, de Wit LT, et al. Segmental resection and wedge excision of the portal or superior mesenteric vein during pancreatoduodenectomy. Surgery 2001;129:158-163. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11174708>.

383. Yu XZ, Li J, Fu DL, et al. Benefit from synchronous portal-superior mesenteric vein resection during pancreaticoduodenectomy for cancer: a meta-analysis. Eur J Surg Oncol 2014;40:371-378. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24560302>.

384. Kelly KJ, Winslow E, Kooby D, et al. Vein involvement during pancreaticoduodenectomy: is there a need for redefinition of "borderline resectable disease"? J Gastrointest Surg 2013;17:1209-1217; discussion 1217. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23620151>.



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385. Traverso LW, Longmire WP, Jr. Preservation of the pylorus in pancreaticoduodenectomy. Surg Gynecol Obstet 1978;146:959-962. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/653575>.

386. Yeo CJ, Cameron JL, Sohn TA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg 1997;226:248-257. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9339931>.

387. van Berge Henegouwen MI, van Gulik TM, DeWit LT, et al. Delayed gastric emptying after standard pancreaticoduodenectomy versus pylorus-preserving pancreaticoduodenectomy: an analysis of 200 consecutive patients. J Am Coll Surg 1997;185:373-379. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9328386>.

388. Kozuschek W, Reith HB, Waleczek H, et al. A comparison of long term results of the standard Whipple procedure and the pylorus preserving pancreatoduodenectomy. J Am Coll Surg 1994;178:443-453. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7909485>.

389. Lin PW, Lin YJ. Prospective randomized comparison between pylorus-preserving and standard pancreaticoduodenectomy. Br J Surg 1999;86:603-607. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10361177>.

390. Matsumoto I, Shinzeki M, Asari S, et al. A prospective randomized comparison between pylorus- and subtotal stomach-preserving pancreatoduodenectomy on postoperative delayed gastric emptying occurrence and long-term nutritional status. J Surg Oncol 2014;109:690-696. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24619624>.

391. Morel P, Mathey P, Corboud H, et al. Pylorus-preserving duodenopancreatectomy: long-term complications and comparison with the Whipple procedure. World J Surg 1990;14:642-646. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2238666>.

392. Roder JD, Stein HJ, Huttli W, Siewert JR. Pylorus-preserving versus standard pancreatico-duodenectomy: an analysis of 110 pancreatic and periampullary carcinomas. Br J Surg 1992;79:152-155. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1348201>.

393. Seiler CA, Wagner M, Sadowski C, et al. Randomized prospective trial of pylorus-preserving vs. Classic duodenopancreatectomy (Whipple procedure): initial clinical results. J Gastrointest Surg 2000;4:443-452. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11077317>.

394. Yeo CJ, Cameron JL, Maher MM, et al. A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. Ann Surg 1995;222:580-588. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7574936>.

395. Topal B, Fieuws S, Aerts R, et al. Pancreaticojejunostomy versus pancreaticogastrostomy reconstruction after pancreaticoduodenectomy for pancreatic or periampullary tumours: a multicentre randomised trial. Lancet Oncol 2013;14:655-662. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23643139>.

396. Wolfgang CL, Pawlik TM. Pancreaticoduodenectomy: time to change our approach? Lancet Oncol 2013;14:573-575. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23643140>.

397. Hallet J, Zih FS, Deobald RG, et al. The impact of pancreaticojejunostomy versus pancreaticogastrostomy reconstruction on pancreatic fistula after pancreaticoduodenectomy: meta-analysis of randomized controlled trials. HPB (Oxford) 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25040921>.

398. Gomez T, Palomares A, Serradilla M, Tejedor L. Reconstruction after pancreatoduodenectomy: Pancreatojejunostomy vs pancreatogastrostomy. World J Gastrointest Oncol 2014;6:369-376. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25232462>.

399. Bassi C, Falconi M, Molinari E, et al. Duct-to-mucosa versus end-to-side pancreaticojejunostomy reconstruction after

pancreaticoduodenectomy: results of a prospective randomized trial. Surgery 2003;134:766-771. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14639354>.

400. Sikora SS, Posner MC. Management of the pancreatic stump following pancreaticoduodenectomy. Br J Surg 1995;82:1590-1597. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8548218>.

401. Strasberg SM, Drebin JA, Mokadam NA, et al. Prospective trial of a blood supply-based technique of pancreaticojejunostomy: effect on anastomotic failure in the Whipple procedure. J Am Coll Surg 2002;194:746-758. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12081065>.

402. Winter JM, Cameron JL, Campbell KA, et al. Does pancreatic duct stenting decrease the rate of pancreatic fistula following pancreaticoduodenectomy? Results of a prospective randomized trial. J Gastrointest Surg 2006;10:1280-1290. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17114014>.

403. Lowy AM, Lee JE, Pisters PW, et al. Prospective, randomized trial of octreotide to prevent pancreatic fistula after pancreaticoduodenectomy for malignant disease. Ann Surg 1997;226:632-641. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9389397>.

404. Yeo CJ, Cameron JL, Lillemoe KD, et al. Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? Results of a prospective randomized placebo-controlled trial. Ann Surg 2000;232:419-429. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10973392>.

405. Allen PJ, Gonen M, Brennan MF, et al. Pasireotide for postoperative pancreatic fistula. N Engl J Med 2014;370:2014-2022. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24849084>.

406. Lillemoe KD, Cameron JL, Kim MP, et al. Does fibrin glue sealant decrease the rate of pancreatic fistula after pancreaticoduodenectomy?

Results of a prospective randomized trial. J Gastrointest Surg 2004;8:766-772. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15531229>.

407. Cubilla AL, Fortner J, Fitzgerald PJ. Lymph node involvement in carcinoma of the head of the pancreas area. Cancer 1978;41:880-887. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/638975>.

408. Nagai H, Kuroda A, Morioka Y. Lymphatic and local spread of T1 and T2 pancreatic cancer. A study of autopsy material. Ann Surg 1986;204:65-71. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3015059>.

409. Glanemann M, Shi B, Liang F, et al. Surgical strategies for treatment of malignant pancreatic tumors: extended, standard or local surgery? World J Surg Oncol 2008;6:123. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19014474>.

410. Pisters P, Brennan M. Regional lymph node dissection for pancreatic adenocarcinoma. In: Evans D, Pisters P, Abbruzzese J, eds., eds. Pancreatic Cancer. New York: Springer-Verlag; 2002:139-151.

411. Pedrazzoli S, DiCarlo V, Dionigi R, et al. Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: a multicenter, prospective, randomized study. Lymphadenectomy Study Group. Ann Surg 1998;228:508-517. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9790340>.

412. Yeo CJ, Cameron JL, Sohn TA, et al. Pancreaticoduodenectomy with or without extended retroperitoneal lymphadenectomy for periaampullary adenocarcinoma: comparison of morbidity and mortality and short-term outcome. Ann Surg 1999;229:613-622; discussion 622-614. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10235519>.

413. Riall TS, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periaampullary

adenocarcinoma--part 3: update on 5-year survival. J Gastrointest Surg 2005;9:1191-1204; discussion 1204-1196. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16332474>.

414. Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periaampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. Ann Surg 2002;236:355-366; discussion 366-358. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12192322>.

415. Nimura Y, Nagino M, Takao S, et al. Standard versus extended lymphadenectomy in radical pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas: long-term results of a Japanese multicenter randomized controlled trial. J Hepatobiliary Pancreat Sci 2012;19:230-241. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22038501>.

416. Michalski CW, Kleeff J, Wente MN, et al. Systematic review and meta-analysis of standard and extended lymphadenectomy in pancreaticoduodenectomy for pancreatic cancer. Br J Surg 2007;94:265-273. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17318801>.

417. Sun J, Yang Y, Wang X, et al. Meta-analysis of the Efficacies of Extended and Standard Pancreatoduodenectomy for Ductal Adenocarcinoma of the Head of the Pancreas. World J Surg 2014;38:2708-2715. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24912627>.

418. Tol JA, Gouma DJ, Bassi C, et al. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). Surgery 2014;156:591-600. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25061003>.

419. Farnell MB, Aranha GV, Nimura Y, Michelassi F. The role of extended lymphadenectomy for adenocarcinoma of the head of the

pancreas: strength of the evidence. J Gastrointest Surg 2008;12:651-656. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18085343>.

420. Shrikhande SV, Barreto SG. Extended pancreatic resections and lymphadenectomy: An appraisal of the current evidence. World J Gastrointest Surg 2010;2:39-46. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21160848>.

421. Cordera F, Arciero CA, Li T, et al. Significance of common hepatic artery lymph node metastases during pancreaticoduodenectomy for pancreatic head adenocarcinoma. Ann Surg Oncol 2007;14:2330-2336. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17492334>.

422. Shimada K, Sakamoto Y, Sano T, Kosuge T. The role of paraaortic lymph node involvement on early recurrence and survival after macroscopic curative resection with extended lymphadenectomy for pancreatic carcinoma. J Am Coll Surg 2006;203:345-352. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16931307>.

423. Bottger TC, Junginger T. Factors influencing morbidity and mortality after pancreaticoduodenectomy: critical analysis of 221 resections. World J Surg 1999;23:164-171. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9880426>.

424. Braasch JW, Gray BN. Considerations that lower pancreatoduodenectomy mortality. Am J Surg 1977;133:480-484. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/848682>.

425. Lerut JP, Gianello PR, Otte JB, Kestens PJ. Pancreaticoduodenal resection. Surgical experience and evaluation of risk factors in 103 patients. Ann Surg 1984;199:432-437. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6712319>.

426. Gundry SR, Strodel WE, Knol JA, et al. Efficacy of preoperative biliary tract decompression in patients with obstructive jaundice. Arch Surg 1984;119:703-708. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6428380>.

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427. Hatfield AR, Tobias R, Terblanche J, et al. Preoperative external biliary drainage in obstructive jaundice. A prospective controlled clinical trial. *Lancet* 1982;2:896-899. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6126752>.

428. Heslin MJ, Brooks AD, Hochwald SN, et al. A preoperative biliary stent is associated with increased complications after pancreatoduodenectomy. *Arch Surg* 1998;133:149-154. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9484726>.

429. Lai EC, Mok FP, Fan ST, et al. Preoperative endoscopic drainage for malignant obstructive jaundice. *Br J Surg* 1994;81:1195-1198. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7741850>.

430. McPherson GA, Benjamin IS, Hodgson HJ, et al. Pre-operative percutaneous transhepatic biliary drainage: the results of a controlled trial. *Br J Surg* 1984;71:371-375. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6372935>.

431. Pitt HA, Gomes AS, Lois JF, et al. Does preoperative percutaneous biliary drainage reduce operative risk or increase hospital cost? *Ann Surg* 1985;201:545-553. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2986562>.

432. Thomas JH, Connor CS, Pierce GE, et al. Effect of biliary decompression on morbidity and mortality of pancreatoduodenectomy. *Am J Surg* 1984;148:727-731. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6439064>.

433. Cavell LK, Allen PJ, Vinoya C, et al. Biliary self-expandable metal stents do not adversely affect pancreatoduodenectomy. *Am J Gastroenterol* 2013;108:1168-1173. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23545711>.

434. van der Gaag NA, Rauws EA, van Eijck CH, et al. Preoperative biliary drainage for cancer of the head of the pancreas. *N Engl J Med* 2010;362:129-137. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20071702>.

435. Pisters PW, Hudec WA, Hess KR, et al. Effect of preoperative biliary decompression on pancreatoduodenectomy-associated morbidity in 300 consecutive patients. *Ann Surg* 2001;234:47-55. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11420482>.

436. Aadam AA, Evans DB, Khan A, et al. Efficacy and safety of self-expandable metal stents for biliary decompression in patients receiving neoadjuvant therapy for pancreatic cancer: a prospective study. *Gastrointest Endosc* 2012;76:67-75. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22483859>.

437. Mullen JT, Lee JH, Gomez HF, et al. Pancreatoduodenectomy after placement of endobiliary metal stents. *J Gastrointest Surg* 2005;9:1094-1104; discussion 1104-1095. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16269380>.

438. Varadhachary GR, Wolff RA, Crane CH, et al. Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 2008;26:3487-3495. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18640929>.

439. Varadhachary GR, Wolff RA. The War on Pancreatic Cancer: Are We Gaining Ground? *Oncology* 2011;24:1335-1336. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21294479>.

440. Krokidis M, Fanelli F, Orgera G, et al. Percutaneous Palliation of Pancreatic Head Cancer: Randomized Comparison of ePTFE/FEP-Covered Versus Uncovered Nitinol Biliary Stents. *Cardiovasc Intervent Radiol* 2010;34:352-361. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20467870>.

441. Kullman E, Frozanpor F, Soderlund C, et al. Covered versus uncovered self-expandable nitinol stents in the palliative treatment of malignant distal biliary obstruction: results from a randomized, multicenter study. *Gastrointest Endosc* 2010;72:915-923. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21034892>.

442. Chun HJ, Kim ES, Hyun JJ, et al. Gastrointestinal and biliary stents. J Gastroenterol Hepatol 2010;25:234-243. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20136988>.

443. Ho H, Mahajan A, Gosain S, et al. Management of complications associated with partially covered biliary metal stents. Dig Dis Sci 2010;55:516-522. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19267200>.

444. Telford JJ, Carr-Locke DL, Baron TH, et al. A randomized trial comparing uncovered and partially covered self-expandable metal stents in the palliation of distal malignant biliary obstruction. Gastrointest Endosc 2010;72:907-914. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21034891>.

445. Lieberman MD, Kilburn H, Lindsey M, Brennan MF. Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy. Ann Surg 1995;222:638-645. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7487211>.

446. Gordon TA, Burleyson GP, Tielsch JM, Cameron JL. The effects of regionalization on cost and outcome for one general high-risk surgical procedure. Ann Surg 1995;221:43-49. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7826160>.

447. Ho V, Heslin MJ. Effect of hospital volume and experience on in-hospital mortality for pancreaticoduodenectomy. Ann Surg 2003;237:509-514. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12677147>.

448. Imperato PJ, Nenner RP, Starr HA, et al. The effects of regionalization on clinical outcomes for a high risk surgical procedure: a study of the Whipple procedure in New York State. Am J Med Qual 1996;11:193-197. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8972936>.

449. Rosemurgy AS, Bloomston M, Serafini FM, et al. Frequency with which surgeons undertake pancreaticoduodenectomy determines length

of stay, hospital charges, and in-hospital mortality. J Gastrointest Surg 2001;5:21-26. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11309644>.

450. Sosa JA, Bowman HM, Gordon TA, et al. Importance of hospital volume in the overall management of pancreatic cancer. Ann Surg 1998;228:429-438. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9742926>.

451. Gouma DJ, van Geenen RC, van Gulik TM, et al. Rates of complications and death after pancreaticoduodenectomy: risk factors and the impact of hospital volume. Ann Surg 2000;232:786-795. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11088073>.

452. Simunovic M, To T, Theriault M, Langer B. Relation between hospital surgical volume and outcome for pancreatic resection for neoplasm in a publicly funded health care system. CMAJ 1999;160:643-648. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10101998>.

453. van Heek NT, Kuhlmann KF, Scholten RJ, et al. Hospital volume and mortality after pancreatic resection: a systematic review and an evaluation of intervention in the Netherlands. Ann Surg 2005;242:781-788, discussion 788-790. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16327488>.

454. Birkmeyer JD, Finlayson SR, Tosteson AN, et al. Effect of hospital volume on in-hospital mortality with pancreaticoduodenectomy. Surgery 1999;125:250-256. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10076608>.

455. Birkmeyer JD, Siewers AE, Finlayson EVA, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346:1128-1137. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11948273>.

456. Bilimoria KY, Bentrem DJ, Ko CY, et al. Multimodality therapy for pancreatic cancer in the U.S. : utilization, outcomes, and the effect of

hospital volume. Cancer 2007;110:1227-1234. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17654662>.

457. La Torre M, Nigri G, Ferrari L, et al. Hospital volume, margin status, and long-term survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. Am Surg 2012;78:225-229. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22369834>.

458. Hyder O, Dodson RM, Nathan H, et al. Influence of patient, physician, and hospital factors on 30-day readmission following pancreatoduodenectomy in the United States. JAMA Surg 2013;148:1095-1102. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/24108580>.

459. Verbeke CS. Resection margins and R1 rates in pancreatic cancer--are we there yet? Histopathology 2008;52:787-796. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18081813>.

460. Tang LH, Berlin J, Branton P, et al. Protocol for the Examination of Specimens from Patients with Carcinoma of the Exocrine Pancreas. 2013. Available at:
http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2013/PancreasEndo_13protocol_3201.pdf.

461. Gebhardt C, Meyer W, Reichel M, Wunsch PH. Prognostic factors in the operative treatment of ductal pancreatic carcinoma. Langenbecks Arch Surg 2000;385:14-20. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/10664114>.

462. Mitsunaga S, Hasebe T, Iwasaki M, et al. Important prognostic histological parameters for patients with invasive ductal carcinoma of the pancreas. Cancer Sci 2005;96:858-865. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16367904>.

463. Huebner M, Kendrick M, Reid-Lombardo KM, et al. Number of lymph nodes evaluated: prognostic value in pancreatic adenocarcinoma. J Gastrointest Surg 2012;16:920-926. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22421988>.

464. Opfermann KJ, Wahlquist AE, Garrett-Mayer E, et al. Adjuvant Radiotherapy and Lymph Node Status for Pancreatic Cancer: Results of a Study From the Surveillance, Epidemiology, and End Results (SEER) Registry Data. Am J Clin Oncol 2014;37:112-116. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23211221>.

465. Valsangkar NP, Bush DM, Michaelson JS, et al. N0/N1, PNL, or LNR? The Effect of Lymph Node Number on Accurate Survival Prediction in Pancreatic Ductal Adenocarcinoma. J Gastrointest Surg 2013;17:257-266. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23229885>.

466. Ashfaq A, Pockaj BA, Gray RJ, et al. Nodal Counts and Lymph Node Ratio Impact Survival After Distal Pancreatectomy for Pancreatic Adenocarcinoma. J Gastrointest Surg 2014. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/24916590>.

467. John BJ, Naik P, Ironside A, et al. Redefining the R1 resection for pancreatic ductal adenocarcinoma: tumour lymph nodal burden and lymph node ratio are the only prognostic factors associated with survival. HPB (Oxford) 2013;15:674-680. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23458477>.

468. Robinson SM, Rahman A, Haugk B, et al. Metastatic lymph node ratio as an important prognostic factor in pancreatic ductal adenocarcinoma. Eur J Surg Oncol 2012;38:333-339. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22317758>.

469. Shamseddine AI, Mukherji D, Melki C, et al. Lymph node ratio is an independent prognostic factor after resection of periampullary malignancies: data from a tertiary referral center in the middle East. Am J Clin Oncol 2014;37:13-18. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23111358>.

470. Wentz SC, Zhao ZG, Shyr Y, et al. Lymph node ratio and preoperative CA 19-9 levels predict overall survival and recurrence-free survival in patients with resected pancreatic adenocarcinoma. World J

Gastrointest Oncol 2012;4:207-215. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23444312>.

471. Classification of pancreatic cancer (ed 2). Tokyo: Kanehara, Japan Pancreas Society 2003.

472. Campbell F, Foulis AK, Verbeke CC. Dataset for the histopathological reporting of carcinomas of the pancreas, ampulla of Vater and common bile duct. The Royal College of Pathologists 2010. Available at:
<http://www.rcpath.org/Resources/RCPPath/Migrated%20Resources/Documents/D/datasethistopathologicalreportingcarcinomasmay10.pdf>.

473. Hruban RH, Pitman MB, Klimstra DS. Tumors of the Pancreas: Afip Atlas of Tumor Pathology; 4th Series Fascicle 6: American Registry of Pathology; Armed Forces Institutes of Pathology; 2007.

474. Konstantinidis IT, Warshaw AL, Allen JN, et al. Pancreatic ductal adenocarcinoma: is there a survival difference for R1 resections versus locally advanced unresectable tumors? What is a "true" R0 resection? Ann Surg 2013;257:731-736. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22968073>.

475. Frampton AE, Gall TM, Krell J, et al. Is there a 'margin' for error in pancreatic cancer surgery? Future Oncol 2013;9:31-34. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23252561>.

476. Gnerlich JL, Luka SR, Deshpande AD, et al. Microscopic margins and patterns of treatment failure in resected pancreatic adenocarcinoma. Arch Surg 2012;147:753-760. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22911074>.

477. Delperio JR, Bachellier P, Regenet N, et al. Pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: a French multicentre prospective evaluation of resection margins in 150 evaluable specimens. HPB (Oxford) 2014;16:20-33. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23464850>.

478. Valle JW, Palmer D, Jackson R, et al. Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: ongoing lessons from the ESPAC-3 study. J Clin Oncol 2014;32:504-512. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/24419109>.

479. Reni M. Neoadjuvant treatment for resectable pancreatic cancer: time for phase III testing? World J Gastroenterol 2010;16:4883-4887. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20954273>.

480. Araujo RL, Gaujoux S, Huguet F, et al. Does pre-operative chemoradiation for initially unresectable or borderline resectable pancreatic adenocarcinoma increase post-operative morbidity? A case-matched analysis. HPB (Oxford) 2013;15:574-580. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23458208>.

481. Lim KH, Chung E, Khan A, et al. Neoadjuvant therapy of pancreatic cancer: the emerging paradigm? Oncologist 2012;17:192-200. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22250057>.

482. Dholakia AS, Hacker-Prietz A, Wild AT, et al. Resection of borderline resectable pancreatic cancer after neoadjuvant chemoradiation does not depend on improved radiographic appearance of tumor-vessel relationships. J Radiat On 2013;2:413-425. Available at: <http://citations.springer.com/item?doi=10.1007/s13566-013-0115-6>.

483. Katz MH, Fleming JB, Bhosale P, et al. Response of borderline resectable pancreatic cancer to neoadjuvant therapy is not reflected by radiographic indicators. Cancer 2012;118:5749-5756. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22605518>.

484. Esnaola NF, Chaudhary UB, O'Brien P, et al. Phase 2 trial of induction gemcitabine, oxaliplatin, and cetuximab followed by selective capecitabine-based chemoradiation in patients with borderline resectable or unresectable locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 2014;88:837-844. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/24606850>.

485. Festa V, Andriulli A, Valvano MR, et al. Neoadjuvant chemo-radiotherapy for patients with borderline resectable pancreatic cancer: a meta-analytical evaluation of prospective studies. Jop 2013;14:618-625. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24216547>.

486. Kim EJ, Ben-Josef E, Herman JM, et al. A multi-institutional phase 2 study of neoadjuvant gemcitabine and oxaliplatin with radiation therapy in patients with pancreatic cancer. Cancer 2013;119:2692-2700. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23720019>.

487. Landry J, Catalano PJ, Staley C, et al. Randomized phase II study of gemcitabine plus radiotherapy versus gemcitabine, 5-fluorouracil, and cisplatin followed by radiotherapy and 5-fluorouracil for patients with locally advanced, potentially resectable pancreatic adenocarcinoma. J Surg Oncol 2010;101:587-592. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20461765>.

488. Marti JL, Hochster HS, Hiotis SP, et al. Phase I/II trial of induction chemotherapy followed by concurrent chemoradiotherapy and surgery for locoregionally advanced pancreatic cancer. Ann Surg Oncol 2008;15:3521-3531. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18830756>.

489. Van Buren G, 2nd, Ramanathan RK, Krasinskas AM, et al. Phase II study of induction fixed-dose rate gemcitabine and bevacizumab followed by 30 Gy radiotherapy as preoperative treatment for potentially resectable pancreatic adenocarcinoma. Ann Surg Oncol 2013;20:3787-3793. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23904005>.

490. McClaine RJ, Lowy AM, Sussman JJ, et al. Neoadjuvant therapy may lead to successful surgical resection and improved survival in patients with borderline resectable pancreatic cancer. HPB (Oxford) 2010;12:73-79. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20495649>.

491. Stokes JB, Nolan NJ, Stelow EB, et al. Preoperative Capecitabine and Concurrent Radiation for Borderline Resectable Pancreatic Cancer.

Ann Surg Oncol 2011;18:619-627. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21213060>.

492. Laurence JM, Tran PD, Morarji K, et al. A Systematic Review and Meta-analysis of Survival and Surgical Outcomes Following Neoadjuvant Chemoradiotherapy for Pancreatic Cancer. J Gastrointest Surg 2011;15:2059-2069. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21913045>.

493. Christians KK, Tsai S, Mahmoud A, et al. Neoadjuvant FOLFIRINOX for Borderline Resectable Pancreas Cancer: A New Treatment Paradigm? Oncologist 2014;19:266-274. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24569947>.

494. Tinchon C, Hubmann E, Pichler A, et al. Safety and efficacy of neoadjuvant FOLFIRINOX treatment in a series of patients with borderline resectable pancreatic ductal adenocarcinoma. Acta Oncol 2013;52:1231-1233. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23445338>.

495. Artinyan A, Anaya DA, McKenzie S, et al. Neoadjuvant therapy is associated with improved survival in resectable pancreatic adenocarcinoma. Cancer 2011;117:2044-2049. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21523715>.

496. Breslin TM, Hess KR, Harbison DB, et al. Neoadjuvant chemoradiotherapy for adenocarcinoma of the pancreas: treatment variables and survival duration. Ann Surg Oncol 2001;8:123-132. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11258776>.

497. Evans DB, Rich TA, Byrd DR, et al. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. Arch Surg 1992;127:1335-1339. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1359851>.

498. Evans DB, Varadhachary GR, Crane CH, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable

adenocarcinoma of the pancreatic head. J Clin Oncol 2008;26:3496-3502. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18640930>.

499. Hoffman JP, Weese JL, Solin LJ, et al. A pilot study of preoperative chemoradiation for patients with localized adenocarcinoma of the pancreas. Am J Surg 1995;169:71-77. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7818001>.

500. Hoffman JP, Lipsitz S, Pisansky T, et al. Phase II trial of preoperative radiation therapy and chemotherapy for patients with localized, resectable adenocarcinoma of the pancreas: an Eastern Cooperative Oncology Group Study. J Clin Oncol 1998;16:317-323. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9440759>.

501. Palmer DH, Stocken DD, Hewitt H, et al. A randomized phase 2 trial of neoadjuvant chemotherapy in resectable pancreatic cancer: gemcitabine alone versus gemcitabine combined with cisplatin. Ann Surg Oncol 2007;14:2088-2096. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17453298>.

502. Spitz FR, Abbruzzese JL, Lee JE, et al. Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodenectomy for adenocarcinoma of the pancreas. J Clin Oncol 1997;15:928-937. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9060530>.

503. Talamonti MS, Small W, Mulcahy MF, et al. A multi-institutional phase II trial of preoperative full-dose gemcitabine and concurrent radiation for patients with potentially resectable pancreatic carcinoma. Ann Surg Oncol 2006;13:150-158. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16418882>.

504. Abbott DE, Tzeng CW, Merkow RP, et al. The cost-effectiveness of neoadjuvant chemoradiation is superior to a surgery-first approach in the treatment of pancreatic head adenocarcinoma. Ann Surg Oncol 2013;20 Suppl 3:S500-508. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23397153>.

505. Palta M, Willett C, Czito B. Role of radiation therapy in patients with resectable pancreatic cancer. Oncology (Williston Park) 2011;25:715-721, 727. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21874833>.

506. Takahashi H, Ogawa H, Ohigashi H, et al. Preoperative chemoradiation reduces the risk of pancreatic fistula after distal pancreatectomy for pancreatic adenocarcinoma. Surgery 2011;150:547-556. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21621236>.

507. Andriulli A, Festa V, Botteri E, et al. Neoadjuvant/preoperative gemcitabine for patients with localized pancreatic cancer: a meta-analysis of prospective studies. Ann Surg Oncol 2012;19:1644-1662. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22012027>.

508. Chua TC, Saxena A. Preoperative chemoradiation followed by surgical resection for resectable pancreatic cancer: a review of current results. Surg Oncol 2011;20:e161-168. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21704510>.

509. Pingpank JF, Hoffman JP, Ross EA, et al. Effect of preoperative chemoradiotherapy on surgical margin status of resected adenocarcinoma of the head of the pancreas. J Gastrointest Surg 2001;5:121-130. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11331473>.

510. Golcher H, Brunner TB, Witzigmann H, et al. Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer : Results of the first prospective randomized phase II trial. Strahlenther Onkol 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25252602>.

511. Tachezy M, Gebauer F, Petersen C, et al. Sequential neoadjuvant chemoradiotherapy (CRT) followed by curative surgery vs. primary surgery alone for resectable, non-metastasized pancreatic adenocarcinoma: NEOPA- a randomized multicenter phase III study (NCT01900327, DRKS00003893, ISRCTN82191749). BMC Cancer

2014;14:411. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/24906700>.

512. Furman MJ, Lambert LA, Sullivan ME, Whalen GF. Rational follow-up after curative cancer resection. J Clin Oncol 2013;31:1130-1133. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23358986>.

513. Tzeng CW, Fleming JB, Lee JE, et al. Yield of clinical and radiographic surveillance in patients with resected pancreatic adenocarcinoma following multimodal therapy. HPB (Oxford) 2012;14:365-372. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22568412>.

514. Tzeng CW, Abbott DE, Cantor SB, et al. Frequency and intensity of postoperative surveillance after curative treatment of pancreatic cancer: a cost-effectiveness analysis. Ann Surg Oncol 2013;20:2197-2203. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23408126>.

515. Witkowski ER, Smith JK, Ragulin-Coyne E, et al. Is it worth looking? Abdominal imaging after pancreatic cancer resection: a national study. J Gastrointest Surg 2012;16:121-128. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21972054>.

516. Tempero MA, Berlin J, Ducreux M, et al. Pancreatic cancer treatment and research: an international expert panel discussion. Ann Oncol 2011;22:1500-1506. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21199884>.

517. Katz MH, Wang H, Fleming JB, et al. Long-term survival after multidisciplinary management of resected pancreatic adenocarcinoma. Ann Surg Oncol 2009;16:836-847. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19194760>.

518. Meyers MO, Meszoely IM, Hoffman JP, et al. Is reporting of recurrence data important in pancreatic cancer? Ann Surg Oncol 2004;11:304-309. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14993026>.

519. Arnaoutakis GJ, Rangachari D, Laheru DA, et al. Pulmonary resection for isolated pancreatic adenocarcinoma metastasis: an analysis of outcomes and survival. J Gastrointest Surg 2011;15:1611-1617. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21725701>.

520. House MG, Choti MA. Palliative therapy for pancreatic/biliary cancer. Surg Clin North Am 2005;85:359-371. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15833477>.

521. Soderlund C, Linder S. Covered metal versus plastic stents for malignant common bile duct stenosis: a prospective, randomized, controlled trial. Gastrointest Endosc 2006;63:986-995. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16733114>.

522. Moss AC, Morris E, Mac Mathuna P. Palliative biliary stents for obstructing pancreatic carcinoma. Cochrane Database Syst Rev 2006:CD004200. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16625598>.

523. Kitano M, Yamashita Y, Tanaka K, et al. Covered self-expandable metal stents with an anti-migration system improve patency duration without increased complications compared with uncovered stents for distal biliary obstruction caused by pancreatic carcinoma: a randomized multicenter trial. Am J Gastroenterol 2013;108:1713-1722. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24042190>.

524. Maire F, Hammel P, Ponsot P, et al. Long-term outcome of biliary and duodenal stents in palliative treatment of patients with unresectable adenocarcinoma of the head of pancreas. Am J Gastroenterol 2006;101:735-742. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16635221>.

525. Lillemoe KD, Cameron JL, Hardacre JM, et al. Is prophylactic gastrojejunostomy indicated for unresectable periampullary cancer? A prospective randomized trial. Ann Surg 1999;230:322-328. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10493479>.

526. Van Heek NT, De Castro SM, van Eijck CH, et al. The need for a prophylactic gastrojejunostomy for unresectable periampullary cancer: a prospective randomized multicenter trial with special focus on assessment of quality of life. *Ann Surg* 2003;238:894-902; discussion 902-895. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14631226>.

527. Lillemoe KD, Cameron JL, Kaufman HS, et al. Chemical splanchnicectomy in patients with unresectable pancreatic cancer. A prospective randomized trial. *Ann Surg* 1993;217:447-455; discussion 456-447. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7683868>.

528. Wyse JM, Carone M, Paquin SC, et al. Randomized, double-blind, controlled trial of early endoscopic ultrasound-guided celiac plexus neurolysis to prevent pain progression in patients with newly diagnosed, painful, inoperable pancreatic cancer. *J Clin Oncol* 2011;29:3541-3546. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21844506>.

529. Wong GY, Schroeder DR, Carns PE, et al. Effect of neurolytic celiac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: a randomized controlled trial. *JAMA* 2004;291:1092-1099. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14996778>.

530. Jeurnink SM, Polinder S, Steyerberg EW, et al. Cost comparison of gastrojejunostomy versus duodenal stent placement for malignant gastric outlet obstruction. *J Gastroenterol* 2010;45:537-543. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20033227>.

531. Jeurnink SM, Steyerberg EW, Hof G, et al. Gastrojejunostomy versus stent placement in patients with malignant gastric outlet obstruction: a comparison in 95 patients. *J Surg Oncol* 2007;96:389-396. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17474082>.

532. Jeurnink SM, van Eijck CH, Steyerberg EW, et al. Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review. *BMC Gastroenterol* 2007;7:18. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17559659>.

533. Gurusamy KS, Kumar S, Davidson BR. Prophylactic gastrojejunostomy for unresectable periampullary carcinoma. *Cochrane Database Syst Rev* 2013;2:CD008533. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23450583>.

534. Gao L, Yang YJ, Xu HY, et al. A randomized clinical trial of nerve block to manage end-stage pancreatic cancerous pain. *Tumour Biol* 2014;35:2297-2301. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24163058>.

535. Zhong W, Yu Z, Zeng JX, et al. Celiac plexus block for treatment of pain associated with pancreatic cancer: a meta-analysis. *Pain Pract* 2014;14:43-51. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23682788>.

536. Dominguez-Munoz JE. Pancreatic enzyme therapy for pancreatic exocrine insufficiency. *Curr Gastroenterol Rep* 2007;9:116-122. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17418056>.

537. Keller J, Laver P. Human pancreatic exocrine response to nutrients in health and disease. *Gut* 2005;54 Suppl 6:vi1-28. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15951527>.

538. Sikkens EC, Cahen DL, Kuipers EJ, Bruno MJ. Pancreatic enzyme replacement therapy in chronic pancreatitis. *Best Pract Res Clin Gastroenterol* 2010;24:337-347. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20510833>.

539. Dominguez-Munoz JE. Pancreatic exocrine insufficiency: diagnosis and treatment. *J Gastroenterol Hepatol* 2011;26 Suppl 2:12-16. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21323992>.

540. Lemaire E, O'Toole D, Sauvanet A, et al. Functional and morphological changes in the pancreatic remnant following pancreaticoduodenectomy with pancreaticogastric anastomosis. *Br J Surg* 2000;87:434-438. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10759738>.

541. Epstein AS, O'Reilly EM. Exocrine pancreas cancer and thromboembolic events: a systematic literature review. J Natl Compr Canc Netw 2012;10:835-846. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22773799>.

542. Khorana AA, Francis CW, Culakova E, et al. Thromboembolism in hospitalized neutropenic cancer patients. J Clin Oncol 2006;24:484-490. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16421425>.

543. Lee AYY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003;349:146-153. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12853587>.

544. Riess H, Pelzer U, Deutschinoff G, et al. A prospective, randomized trial of chemotherapy with or without the low molecular weight heparin (LMWH) enoxaparin in patients (pts) with advanced pancreatic cancer (APC): Results of the CONKO 004 trial [abstract]. J Clin Oncol 2009;27(suppl):LBA4506. Available at: <http://meeting.ascopubs.org/cgi/content/abstract/27/18S/LBA4506?sid=e598f786-51a5-42d1-82a4-08d6f1163f76>.

545. Boyd AD, Brown D, Henrickson C, et al. Screening for depression, sleep-related disturbances, and anxiety in patients with adenocarcinoma of the pancreas: a preliminary study. ScientificWorldJournal 2012;2012:650707. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22666142>.

546. Turaga KK, Malafa MP, Jacobsen PB, et al. Suicide in patients with pancreatic cancer. Cancer 2011;117:642-647. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20824626>.

547. Philip PA, Mooney M, Jaffe D, et al. Consensus report of the national cancer institute clinical trials planning meeting on pancreas cancer treatment. J Clin Oncol 2009;27:5660-5669. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19858397>.

548. Van Laethem JL, Verslype C, Iovanna JL, et al. New strategies and designs in pancreatic cancer research: consensus guidelines report from a European expert panel. Ann Oncol 2012;23:570-576. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21810728>.

549. Tempero MA, Klimstra D, Berlin J, et al. Changing the Way We Do Business: Recommendations to Accelerate Biomarker Development in Pancreatic Cancer. Clin Cancer Res 2013;19:538-540. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23344262>.

550. Ellis LM, Bernstein DS, Voest EE, et al. American society of clinical oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol 2014;32:1277-1280. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24638016>.

551. Philip PA, Chansky K, LeBlanc M, et al. Historical controls for metastatic pancreatic cancer: benchmarks for planning and analyzing single-arm phase II trials. Clin Cancer Res 2014;20:4176-4185. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24914040>.

552. Varadhachary GR, Evans DB. Rational study endpoint(s) for preoperative trials in pancreatic cancer: pathologic response rate, margin negative resection, overall survival or 'all of the above'? Ann Surg Oncol 2013;20:3712-3714. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23943023>.

553. Pogue-Geile KL, Chen R, Bronner MP, et al. Palladin mutation causes familial pancreatic cancer and suggests a new cancer mechanism. PLoS Med 2006;3:e516. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17194196>.

554. Wayne JD, Abdalla EK, Wolff RA, et al. Localized adenocarcinoma of the pancreas: the rationale for preoperative chemoradiation. Oncologist 2002;7:34-45. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11854545>.

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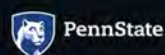
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Appendix OBERSTEIN02

Pancreatic cancer: why is it so hard to treat?

Paul E. Oberstein and Kenneth P. Olive

Abstract: No common malignancy is as rapidly and inevitably fatal as pancreatic ductal adenocarcinoma (PDA). This grim fact has driven substantial research efforts into this disease in recent decades. Unfortunately, the investment has yet to result in a meaningful increase in 5-year survival. This has prompted many pancreatic cancer researchers and advocates to redouble their efforts, but also requires one to step back and ask why the previous efforts were lacking and to consider why pancreatic cancer is so difficult to treat. The difficulties are legion. PDA is characterized by an insidious clinical syndrome, but is rarely diagnosed at a time when surgical resection is feasible. We lack markers of early detection and screening programs remain unproven even in high risk populations. The location of the tumor in the retroperitoneum, the advanced age of patients, and the systemic effects of disease limit the options for local therapy. Chemotherapy may provide a small benefit, but most efforts to improve on the current regimens consistently and stubbornly fail in advanced clinical trials. The molecular and cellular features of ductal pancreatic tumors are aggressive and underlay multiple levels of therapeutic resistance. Non-cell-autonomous features including stromal proliferation, reduced vascular density and immune suppression also contribute to therapeutic resistance. Growing awareness of these the fundamental features of PDA has begun to guide ongoing research efforts. Clinical trials are now specifically targeting these tumor properties and actively focusing on the therapeutic implications of tumor stroma. As reviewed here, reflecting on the fundamental question of why pancreatic cancer is so difficult to treat is a necessary and informative exercise that will aid our efforts to improve patient outcomes. These efforts will lead to improvements in clinical trial design, expand our focus to include the molecular and histologic implications of novel treatment paradigms, and ultimately change the lives of our patients.

Keywords: pancreatic cancer, chemotherapy resistance, tumor desmoplasia

Introduction

In the modern era of cancer research, pancreatic ductal adenocarcinoma (PDA) has proven to be among the most unyielding of adversaries. The oncology community has expended its entire arsenal at this disease with little effect: the 5-year survival rate has ticked up to 6% over the past 40 years, but nearly all diagnosed patients ultimately succumb to the disease. An estimated 37,390 people will die of pancreatic cancer in the US in 2012 [Siegel *et al.* 2012] with a similar pattern in the rest of the developed world [Jemal *et al.* 2011]. Over 80% of them will be found to have unresectable tumors at diagnosis [Stathis and Moore, 2010], giving them an expected overall survival of just 6 months. There are few therapeutic options

for these patients and the most efficacious are also the most burdensome. Those who do undergo surgery improve their overall survival compared with patients of a similar stage by about 10 months [Bilimoria *et al.* 2007], but must tolerate significant morbidity and face almost inevitable recurrence. Given the slow progress against this disease, one must ask the question ‘why is pancreatic cancer so hard to treat?’.

The particular problem of pancreatic cancer is multifactorial in its nature. The patient population in PDA is predominantly elderly and in poor overall health. There is no simple early detection method for pancreatic cancer and the earliest indications of disease are nonspecific. The tumor

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itself has its own peculiarities. For example, it has become apparent that PDA metastasizes microscopically early in the disease course, limiting the effectiveness of local therapies such as surgery and radiation. At the cellular level, the actual neoplastic epithelial cells at the heart of the disease harbor some of the most profoundly oncogenic alterations known to biology, and these are found at unusually high frequencies in PDA. In addition to driving growth and promoting cell survival, these alterations alter the metabolism of pancreatic cancer to one that can better support the manufacture of new cellular components. Layered on top of these high penetrance mutations is a host of rare alterations that are found in effectively unique combinations in each patient. The extent of genetic alterations in pancreatic tumors bears witness to a genomic instability phenotype that appears to play a significant role in the biology of PDA and implies an ability to rapidly develop acquired resistance to therapies that do manage to provoke an initial response. In addition to features of the tumor epithelium, PDA harbors a dense, desmoplastic stroma that can serve to limit the delivery of agents to tumors and foreshadows an incredibly complex interplay of intercellular signals that confound our ability to study the disease *in vitro*. Certain cell types within this stroma construct an immune-suppressed microenvironment that prevents the local immune system from clearing the tumor. Finally, PDA manifests as a syndrome, not just a mass, with systemic comorbidities that have a profoundly negative impact on quality of life.

Together, these raw observations paint a grim picture of the battle against pancreatic cancer that has at times led to a sense of nihilism. In reality, there are many signs that the research efforts of the past few decades have altered the momentum of this battle. Each of the challenges listed above has, in recent years, been the subject of intense research, leading to new ideas that are now being developed in the lab and in the clinic. For example, an understanding of the dynamics of drug delivery in PDA has led to a focus on targeted agents with desirable pharmacological properties. Another approach is to target the tumor stroma directly in order to facilitate the delivery of genotoxic agents or relieve local immune suppression. Other agents take advantage of the hypoxic microenvironment conferred by the desmoplastic stroma, or specific metabolic dependencies. Furthermore, decades of failed trials have led to improvements in clinical trial design and in the diagnostic and interventional techniques used in patients. By

addressing the manifold difficulties that underpin the challenge of pancreatic cancer, a new sense of optimism is apparent. These barriers are surmountable and the nascent efforts to address them will ultimately be reflected in improved patient outcomes.

Patient population and diagnosis

Pancreatic ductal adenocarcinoma is largely a disease of old age, with an average age of diagnosis of 71 years. Yet the presenting symptoms are nonspecific such as weight loss and abdominal pain [Bakkevold *et al.* 1992]. This population of patients (and their general practitioners) is accustomed to aches and pains, and so in most cases, the earliest signs of malignancy go unnoticed; a high level of perception is required to avoid delays in diagnostic workup. Furthermore, in contrast to breast, prostate, melanoma and testicular cancers, there are no simple examinations that can elevate the level of suspicion: the pancreas is too deep to palpate and there is no specific blood test available for PDA. Other symptoms at diagnosis can include new onset of diabetes [Chari *et al.* 2005], unexplained jaundice [Porta *et al.* 2005] and unprovoked thrombosis [Khorana and Fine, 2004]; the most specific of these is unexplained painless jaundice, but many other explanations are possible. Thus, by the time that a patient seeks medical advice and their GP successfully navigates the diagnostic maze, often many months have passed and the patient's condition has further deteriorated.

PDA is associated with a syndrome of comorbidities that affect patients' overall health and in some cases can be life threatening. Symptoms related to pain [Porta *et al.* 2005] and depression [Kelsen *et al.* 1995] are components of this syndrome and are often present at the time of diagnosis, but become more severe with progression of the disease. PDA is intrinsically associated with biliary obstruction, infection, jaundice, ascites and pancreatic insufficiency, but beyond these factors PDA patients frequently experience the hypercatabolic state of cachexia and muscle wasting [Pausch *et al.* 2012]. In addition, PDA is classically associated with hypercoagulability and development of thromboembolic disease (Trousseau's syndrome) [Khorana and Fine, 2004]. Combined with the host of unrelated ailments typical of patients in their seventh, eighth and ninth decades of life, the average condition of PDA patients is poor, and many in this population may never be eligible or receive therapy.

From an epidemiological standpoint, efforts to change the long-term outcome of PDA patients through modification of risk factors have also been disappointing. Few behaviors reliably predict an increased risk for PDA [Raimondi *et al.* 2009]. Of those factors, cigarette use [Iodice *et al.* 2008; Heinen *et al.* 2010] should be discouraged but others, such as dietary habits, are less definitive [Thiebaut *et al.* 2009] and there is not sufficient evidence to recommend dietary changes to reduce the risk of PDA. The most promising chemopreventative agent is low-dose aspirin, which has been shown to significantly reduce the risk of pancreatic cancer in a dose-dependent manner [Tan *et al.* 2011]. There are familial clusters of PDA [Hruban *et al.* 1999; Bartsch *et al.* 2004; Shi *et al.* 2009] and first-degree relatives of affected patients are at increased risk [Klein *et al.* 2004; Hruban *et al.* 2010]. However, these comprise a minority of the overall population of PDA patients (5–10%) [Bartsch *et al.* 2012].

Furthermore, this knowledge is of limited benefit due to the lack of validated screening tests for early diagnosis of PDA. Due to its location in the retroperitoneum, the pancreas is difficult to access and sample with traditional endoscopic techniques. Endoscopic ultrasound techniques provide for higher yields but the morbidity associated with this procedure makes it unsuitable as a screening tool in an unselected population. Studies are ongoing in targeted populations of patients at high risk [Langer *et al.* 2009; Verna *et al.* 2010; Canto *et al.* 2012]. Cross-sectional imaging has the potential to identify small and even asymptomatic pancreatic lesions while they are still amenable to surgical resection [Canto *et al.* 2012]. However, due to poor innate contrast between PDA and the surrounding pancreas, specialized imaging protocols are required to optimally image pancreatic cancer by computerized tomography (CT) and magnetic resonance imaging (MRI) [Erkan *et al.* 2012]. As discussed later, PDA is characterized by hypovascularity and reduced perfusion compared with normal pancreatic tissue and this property may be utilized to obtain greater resolution in the detection of early lesions using techniques such as diffusion-weighted MRI [Holzapfel *et al.* 2011].

Serum sampling has not yet identified a suitable screening test for early detection of PDA. Many pancreatic lesions secrete CA19-9 (carbohydrate antigen 19-9) and this serum assay has a role in some patients in monitoring disease activity and response to therapy [Steinberg, 1990]. However

CA19-9 has little use alone as a screening test due to high rates of false positivity in patients with non-malignant hepatobiliary disease [Frebours *et al.* 1988]. There are ongoing efforts to identify molecular markers for early diagnosis of PDA [Goggins, 2005] but so far there are no validated agents and, as a consequence, diagnosis is often delayed.

The limited effect of local therapies

Currently, complete surgical resection provides the only potential for long-term cure of PDA but only a minority of patients have tumors that are amenable to surgery [Shaib *et al.* 2006]. This is due to the fact that, upon diagnosis, tumors have generally spread to involve critical abdominal vessels as well as adjacent organs. Significant advances have been made in the technical aspects of surgical resection with decreases in short-term morbidity and mortality at major centers [Winter *et al.* 2012]. Yet even in the most experienced centers, long-term survival after surgery is poor [Farnell *et al.* 2005; Ferrone *et al.* 2012], with tumors recurring in virtually all patients [Allison *et al.* 1998]. Due to the high rate of recurrence, local targeted therapy with radiation has been suggested following surgery. However, controlled studies of the long-term impact of adjuvant radiation therapy have proved inconclusive to date [Neoptolemos *et al.* 2004]. The cytotoxic effect of radiation therapy relies in part on the presence of oxygen [Harrison *et al.* 2002]. However, intraoperative oxygen measurements on human patients have found that these tumors are extremely hypoxic [Koong *et al.* 2000], which may contribute to the limited impact of this modality.

The limited long-term efficacy of surgery and adjuvant radiation therapy has led many to conclude that residual tumor tissue remains even in the case of complete surgical resection with no evidence of residual tumor. One possible explanation is that of ‘field effect’ mutations that may affect otherwise normal appearing cells present in the residual pancreatic tissue. Alternatively, PDA may simply metastasize at a microscopic level at a very early stage. Indeed, provocative data in a genetically engineered mouse model of PDA suggest that mutant cells may delaminate from the pancreatic epithelium and enter circulation in the very early stages of tumorigenesis even prior to the development of an overt carcinoma [Rhim *et al.* 2012]. If this is true, then PDA should be considered an inherently metastatic disease for which local therapy is simply a delaying action. This also highlights

the importance of identifying chemotherapeutic agents that effectively target microscopic metastases. It is notable that mutation evolution analysis based on deep sequencing of human pancreatic tumor samples has suggested a long latency period for PDA, estimating that it may take an average of 17 years for a tumor to evolve from a single common progenitor [Yachida *et al.* 2010]. However, a computational modeling study is consistent with the notion that PDA metastasizes early in disease [Haeno *et al.* 2012].

Clinical data of therapeutic efforts following resection of PDA are summarized in Table 1. These trials are consistent in demonstrating a small benefit when assessing recurrence but limited impact on long-term survival regardless of the intervention [Neoptolemos *et al.* 2004, 2010; Stocken *et al.* 2005; Oettle *et al.* 2007]. The modest achievements of adjuvant therapy compare poorly with the experience in other common cancers. Unfortunately PDA cells display broad and intractable resistance to chemotherapy, the subject of the remainder of this review.

Chemotherapy resistance in PDA

The track record of the clinical trials in advanced and metastatic pancreatic cancer is dismal (summarized in Table 2). Gemcitabine and erlotinib (Tarceva) remain the only two agents approved for use in advanced disease despite their modest benefits. Gemcitabine was approved on the basis of a study [Burris *et al.* 1997] showing that it was superior to 5-FU (5-fluorouracil) in providing a clinical benefit among advanced PDA patients with pain symptoms (clinical benefit rate = 23.8% *versus* 4.8%; $p = 0.0022$) and modestly prolonged median survival from 4.4 to 5.6 months ($p = 0.0025$). The incremental median survival benefit seen with the addition of erlotinib to gemcitabine is even smaller (5.9 to 6.2 months, $p = 0.038$), albeit statistically significant [Moore *et al.* 2007].

As summarized in Table 2, over 20 phase III trials have been conducted to improve on the modest efficacy of gemcitabine and these have been overwhelmingly disappointing. These trials covered traditional chemotherapeutic agents and combinations, targeted therapies such as the anti-vascular endothelial growth factor (anti-VEGF) monoclonal antibody, bevacizumab [Kindler *et al.* 2010] and the anti-epidermal growth factor receptor (anti-EGFR) antibody, cetuximab [Philip *et al.* 2010], as well as experimental targeted therapies including

farnesyltransferase inhibitors [van Cutsem *et al.* 2004]. It is difficult to overstate the physical, financial and psychological costs of these unsuccessful attempts.

Two notable exceptions to this tale have been reported in the past 2 years. In 2011, a robust clinical benefit was found in a phase III randomized trial of FOLFIRINOX (a four-drug combination of 5-FU, leucovorin, oxaliplatin and irinotecan) compared with gemcitabine in metastatic PDA (median overall survival [OS] of 11.1 *versus* 6.8 months; $p \leq 0.001$) [Conroy *et al.* 2011]. However, this advantage comes at the cost of significant toxicity, making the regimen appropriate only for those patients with good performance status. As recently as November 2012, after exciting phase II results [von Hoff *et al.* 2011], a phase III trial of nab-paclitaxel (Abraxane) plus gemcitabine was reported to have met its primary overall survival endpoint. We look forward to learning the magnitude of this effect in the coming months and are excited at the prospect of having a range of chemotherapeutic tools to treat patients in different states of health.

This collective history has delivered a consistent overarching message: the response of PDA to chemotherapy is poor. Using standard criteria that define radiographic response as a decrease of 30% (or 50% in older studies) in tumor size, very few patients treated with chemotherapy experience an objective response (noted in Table 2). Thus, the initial resistance of these tumors is primary (innate), rather than the secondary (acquired) resistance that is classically observed in most cancers. This is an important clue to understanding the recalcitrant nature of pancreatic cancer.

Cell-autonomous mechanisms of resistance to chemotherapy

It is informative to think of the resistance of PDA to chemotherapy as occurring due to cell-autonomous and non-cell-autonomous pathways. Although ductal pancreatic tumors display clinical and pathologic heterogeneity, a striking characteristic of PDA is the consistent pattern of high penetrance genetic alterations that occur in four genetic loci: K-ras, p53, cdkn2a and smad4/DPC4. Over 90% of pancreatic tumors harbor activating mutations in K-ras, one of the most potent of all human oncogenes, far exceeding the rate of any other cancer [Almoguera *et al.* 1988; Pellegata *et al.* 1994; Hezel *et al.* 2006; Maitra and Hruban, 2008]. Mutant K-ras initiates a signal

Table 1. Phase III trials of adjuvant therapy following resection of PDA and comparison with other common tumors.

Study	Study period	Study population	Treatment arm(s)	Survival		
				Median OS (months)	<i>p</i> value	5-year survival %
EORTC 40891 [Klinkenbijl <i>et al.</i> 1999]	1987–1995	Stage 1–3 resected PDA (others excluded from this analysis)	Observation Chemoradiotherapy (5-FU based)	12.6 17.1	NS	10 20
ESPAC-1 [Neoptolemos <i>et al.</i> 2004]	1994–2000	Stage 1–3 resected PDA	Observation Chemotherapy alone (5-FU) Chemoradiotherapy Chemoradiotherapy + chemotherapy	16.9 21.6 13.9 19.9	0.009 (for chemo <i>versus</i> no chemo)	11 29 7 13
CONKO-001 [Oettle <i>et al.</i> 2007]	1998–2004	Stage 1–3, resected PDA	Observation Chemo (gemcitabine)	20.7 22.1	NS	11.5 22.5
RTOG 9704 [Regine <i>et al.</i> 2008, 2011]	1998–2002	Stage 1–3, resected PDA in head of pancreas.	5-FU + chemoradiotherapy Gemcitabine + chemoradiotherapy	16.9 20.5	NS	22 18
ESPAC-3 [Neoptolemos <i>et al.</i> 2010]	2000–2007	Stage 1–3, resected PDA	5-FU Gemcitabine	23.0 23.6	NS	NR NR
Lung cancer				mOS		5 year survival
ANITA [Douillard <i>et al.</i> 2006]		Stage IB–IIIA resected, NSCLCa	Observation Chemotherapy	43.7 65.7	0.017	43 51
Colon cancer						6 year survival
MOSAIC [Andre <i>et al.</i> 2004, 2009]	1998–2001	Stage II–III, resected colon cancer	Chemotherapy (FOLFOX)	NR		78.5
Breast cancer						5 year survival
[Sparano <i>et al.</i> 2008]	1999–2002	Stage II–III breast cancer	Chemotherapy (most effective group)	NR		89.7
5-FU: fluorouracil; chemo: chemotherapy; NR: not reported; NS: not significant (<i>p</i> > 0.05); NSCLCa: non-small cell lung cancer. OS: overall survival; PDA: pancreatic ductal adenocarcinoma.						

5-FU: fluorouracil; chemo: chemotherapy; NR: not reported; NS: not significant ($p > 0.05$); NSCLCa: non-small cell lung cancer. OS: overall survival; PDA: pancreatic ductal adenocarcinoma.

transduction cascade that provides a strong pro-growth signal, increases cell motility and invasion, and profoundly rearranges cell metabolism to a growth-promoting state. In pancreatic cancer, Ras mutation initiates paracrine signals that promote and maintain stromal desmoplasia, a key mediator of non-cell-autonomous resistance (see below). Unfortunately, K-ras is an extremely challenging therapeutic target for which no effective targeted inhibitors have been identified to date.

Overlaid on this oncogenic scaffold are mutations in four extremely potent tumor suppressor genes. The *cdkn2a* locus encodes two tumor suppressor genes, *p16^{Ink4a}* and *p15^{ARF}*. These genes are

inactivated through a variety of mechanisms in >90% of human pancreatic tumors [Caldas *et al.* 1994; Schutte *et al.* 1997]. The *p53* tumor suppressor gene is another major tumor suppressor and is altered in 75–90% of pancreatic tumors [Pellegata *et al.* 1994; Redston *et al.* 1994], resulting in impaired DNA damage responses, impaired apoptosis, loss of cell cycle control, and promotion of genomic instability. *p53* is typically altered through ‘gain of function’ missense mutations that may further promote cancer beyond the loss of classical *p53* tumor suppressor functions [Olive *et al.* 2004; Morton *et al.* 2010]. Alterations in *DPC4* [Hahn *et al.* 1996a, 1996b] are observed in more than half of cases and confer a prometastatic phenotype. The combined effect of these mutations

Table 2. Phase III randomized trials with gemcitabine comparison in advanced PDA.

Study*	Accrual period	Number of patients	Treatment groups	Median OS		Response rate	
				Months	<i>p</i>	%	<i>p</i>
[Burris <i>et al.</i> 1997]	1992-1994	126	5-FU	4.4	0.0025	0	NS
			Gemcitabine	5.6		5.4	
[Bramhall <i>et al.</i> 2001]	1997-1998	239	Gem	5.5	NS	11	NS
			G + marimistat	5.5		16	
[Moore <i>et al.</i> 2003]	1997-1999	277	Gem	6.6	<0.001	NR	
			G + BAY 12-9566 (MMP inhibitor)	3.7		NR	
[Heinemann <i>et al.</i> 2006]	1997-2002	195	Gem	6.0	NS	8.2	NS
			G + cisplatin	7.5		10.2	
[Berlin <i>et al.</i> 2002]	1998-1999	322	Gem	5.4	NS	5.6	NS
			G + 5-FU	6.7		6.9	
[Van Cutsem <i>et al.</i> 2004]	1999-2001	688	Gem	6.1	NS	8	NS
			G + tipifarnib	6.4		6	
[Rocha Lima <i>et al.</i> 2004]	2000-2001	360	Gem	6.6	NS	4.1	<0.001
			G + irinotecan	6.3		16.1	
[Louvvet <i>et al.</i> 2005]	2001-2003	313	Gem	7.1	NS	17.3	0.044
			G + oxaliplatin	9.0		26.8	
[Herrmann <i>et al.</i> 2007]	2001-2004	319	Gem	7.2	NS	7.8	NS
			G + capecitabine	8.4		10	
[Abou-Alfa <i>et al.</i> 2006]	2001-2003	349	Gem	6.2	NS	5.2	NS
			G + exatecan	6.7		6.8	
[Moore <i>et al.</i> 2007]	2001-2003	569	Gem	5.9	0.038	8.0	NS
			G + erlotinib	6.2		8.6	
[Oettle <i>et al.</i> 2005]	2001-2003	565	Gem	6.3	NS	7.1	0.004
			G + pemetrexed	6.2		14.8	
[Colucci <i>et al.</i> 2010]	2002-2007	400	Gem	8.3	NS	10.1	NS
			G + cisplatin	7.2		12.9	
[Cunningham <i>et al.</i> 2009]	2002-2005	533	Gem	6.2	NS	12.4	0.034
			G + capecitabine	7.1		19.1	
[Poplin <i>et al.</i> 2009]	2003-2005	832	Gem (standard rate)	4.9	NS	6	NS
			Gem-FDR	6.2		10	
			Gem-FDR + oxaliplatin	5.7		9	
[Philip <i>et al.</i> 2010]	2004-2006	745	Gem	5.9	NS	7	NS
			G + cetuximab	6.3		8	
[Kindler <i>et al.</i> 2010]	2004-2006	602	Gem	5.9	NS	10	NS
			G + bevacizumab	5.8		13	
[Van Cutsem <i>et al.</i> 2009]	2005-2006	607	Gem + erlotinib	6.0	NS	8.6	NS
			Gem + erlotinib + bevacizumab	7.1		13.5	
[Conroy <i>et al.</i> 2011]	2005-2009	342	Gem	6.8	<0.001	9.4	<0.001
			FOLFIRINOX	11.1		31.6	
[Heinemann <i>et al.</i> 2012]	2006-2008	281	Gem + erlotinib (capecitabine for second line)	6.2	NS	16	NR
			Capecitabine + erlotinib (gem for second line)	6.9		5	

(Continued)

Table 2. (Continued)

Study*	Accrual period	Number of patients	Treatment groups	Median OS		Response rate	
				Months	<i>p</i>	%	<i>p</i>
[Goncalves <i>et al.</i> 2012]	2006-2009	104	Gem G + sorafenib	9.2 8	NS	19 23	NS
[Kindler <i>et al.</i> 2011]	2007-2008	632	Gem G + axitinib	8.3 8.5	NS	2 5	0.018

5-FU: fluorouracil; FDR: fixed dose rate. G and Gem: gemcitabine; NR: not reported; NS: not statistically significant ($p > 0.05$);
 *In addition to these trials, several phase III trials have been completed or terminated and remain unpublished. These include fluorouracil plus triacetylruridine [ClinicalTrials.gov identifier: NCT24427], aflibercept [ClinicalTrials.gov identifier: NCT574275], TS-1 [ClinicalTrials.gov identifier: NCT498225], GV1001 vaccine [ClinicalTrials.gov identifier: NCT358566], virulizin [ClinicalTrials.gov identifier: NCT40092] and AMG 479- ganitumab [ClinicalTrials.gov identifier: NCT1231347].

is formidable and likely explains a large portion of the difficulty in treating this disease. Indeed, patients with three or four of these alterations in their tumors have a much worse prognosis than those with one or two (median survival of 9 *versus* 23 months) [Yachida *et al.* 2012].

Besides these well-established ‘driver’ variations, many other genetic changes occur at lower frequencies [Hansel *et al.* 2003; Jones *et al.* 2008; Biankin *et al.* 2012; Perez-Mancera *et al.* 2012]. An effort to sequence the entire exome of 24 PDA samples revealed that the average PDA contains more than 60 genomic changes [Jones *et al.* 2008]. Some of these may contribute to the specific resistance to chemotherapy in as yet unidentified ways. This high degree of genomic changes seen in PDA is suggestive of significant genomic instability and may limit the effectiveness of therapy, especially targeted agents, by contributing to secondary or acquired chemoresistance.

Despite the survival benefits observed in clinical studies, only 5–10% of pancreatic tumors exhibit a radiographic response to gemcitabine therapy. Pharmacological investigations into the mechanisms of gemcitabine activity have led to some of the best characterized determinants of patient prognosis. Gemcitabine [2',2'-difluorodeoxycytidine (dFdC)] is a nucleoside analog of cytidine that must be actively transported into cells and then sequentially phosphorylated to the active triphosphate [2',2'-difluorodeoxycytidine triphosphate (dFdCTP)] [Heinemann *et al.* 1988, Mini *et al.* 2006]. Transport across the cell membrane is primarily mediated by human equilibrative nucleoside transporter (hENT1), though other transporters play a minor role [Mackey *et al.* 1998,

Mini *et al.* 2006]. Cell lines that are resistant to gemcitabine are often hENT1 deficient [Achiwa *et al.* 2004] and hENT1 expression in human tissues can predict response to gemcitabine [Oguri *et al.* 2007]. In pancreatic cancer, patients with elevated hENT1 have improved survival when treated with gemcitabine but not among untreated patients [Marechal *et al.* 2012]. In a large clinical trial [Farrell *et al.* 2009], patients treated with gemcitabine who had no hENT1 staining had poorer survival than those with positive hENT1 staining (hazard ratio for survival = 0.51, 95% confidence interval [CI] = 0.29–0.91; $p = 0.02$).

Enzymes associated with the metabolic activation and inactivation of gemcitabine may also impact tumor sensitivity. The monophosphorylation of gemcitabine is a rate-limiting step in its activation and is mediated by deoxycytidine kinase (dCK). Reduced levels of dCK are associated with gemcitabine resistance in some tumor cell lines [Achiwa *et al.* 2004], while elevated dCK expression is associated with improved survival among those receiving adjuvant gemcitabine in PDA [Marechal *et al.* 2012]. Conversely, gemcitabine can be deaminated to its inactive metabolite [2',2'-difluorodeoxyuridine (dFdU)] in a process catalyzed by the enzyme cytidine deaminase (CDA) [Eliopoulos *et al.* 1998], levels of which are a key determinant of gemcitabine activity. One frequent polymorphism 79A>C (Lys27Gln) is associated with decreased enzymatic activity, improved clinical outcomes, and increased toxicity in combination therapy with gemcitabine in lung cancer [Tibaldi *et al.* 2008]. In pancreatic cancer, the data are conflicting; one group failed to find an effect of this polymorphism on gemcitabine activity [Sugiyama *et al.* 2007], while another group saw increased toxicity but no change in

outcomes in patients with intact CDA treated with gemcitabine [Farrell *et al.* 2012]. Other polymorphisms have also been identified [Sugiyama *et al.* 2007; Tanaka *et al.* 2010] and may be clinically relevant. Other studies suggest that the most relevant measure of CDA is functional testing which can predict rate of severe toxicity to gemcitabine [Ciccolini *et al.* 2010], though the clinical implications of these findings await validation in prospective trials [Giovannetti *et al.* 2010]. It is the high levels of CDA in human plasma that leads to the short (~15 minute) half-life of gemcitabine. This short half-life is compounded by non-cell-autonomous features of pancreatic tumors that limit the delivery of drugs to pancreatic tissues.

Non-cell-autonomous barriers to drug efficacy

A defining characteristic of PDA is the presence of a dense fibrotic proliferation surrounding the epithelial cells that may form the majority of the tumor mass [Chu *et al.* 2007; Neesse *et al.* 2011]. This 'desmoplastic reaction' is composed of various leukocytes, fibroblasts, endothelial cells and neuronal cells, as well as extracellular matrix components such as collagen and hyaluronan. The desmoplastic reaction is driven by paracrine signals originating in the epithelial compartment. These signals are driven by the oncogenic signals such as those initiated by mutant K-ras. A pair of studies in genetically engineered mouse models that utilized 'switchable' alleles of mutant K-ras found that the loss of mutant K-ras expression led to rapid quiescence and involution of the stroma over the course of just a few days [Collins *et al.* 2012; Ying *et al.* 2012]. In recent years, significant effort has been invested in identifying the signals that mediate the relationships between the different cell types in pancreatic tumors. For example, early in pancreatic tumor development, the neoplastic epithelial cells begin to overexpress Sonic Hedgehog (SHH), a secreted ligand that normally plays a role during organ development [Berman *et al.* 2003]. This upregulation has no effect on hedgehog pathway activity in the epithelial compartment [Nolan-Stevaux *et al.* 2009]. Rather, SHH activates the pathway in nearby stromal fibroblasts, promoting their activation and proliferation [Bailey *et al.* 2008; Tian *et al.* 2009]. This pathway has served as a paradigm for how tumor cells influence the behavior of their neighboring stromal cells.

The desmoplastic stroma of pancreatic cancer has physiological effects on the tumor that have a

direct impact on drug efficacy. In contrast to many tumors that are dependent on neo-angiogenesis, ductal pancreatic tumors are very poorly vascularized relative to normal tissues and consequently poorly perfused [Olive *et al.* 2009]. Indirect evidence suggests that this is mediated by an anti-angiogenic effect of the tumor stroma, though the precise mechanism is an area of active research. Regardless, the poor perfusion of pancreatic tumors has the unfortunate consequence of limiting the delivery of therapeutic agents into the tumor parenchyma. Indeed, studies in a genetically engineered mouse model found that the delivery of two different chemotherapeutic agents, gemcitabine and doxorubicin, was approximately one third that of surrounding normal tissues [Olive *et al.* 2009]. Furthermore, poor perfusion in pancreatic tumors has been correlated with poor prognosis in patients [Komar *et al.* 2009]. The drug delivery effect is visualized every time a contrast agent is used to image a patient with pancreatic cancer: the finding of a 'hypo-enhancing mass' in the pancreas is diagnostic for pancreatic ductal adenocarcinoma, particularly compared with endocrine carcinomas of the pancreas, which are hyperperfused [Fusaroli *et al.* 2010; Matsubara *et al.* 2011; Saftoiu *et al.* 2012]. Another consequence of poor perfusion is a hypoxic microenvironment, which can have important effects on radiosensitivity, cell metabolism and cell invasion. Direct measurements of oxygen partial pressure in human pancreatic tumors found that pancreatic tumors are profoundly hypoxic [Koong *et al.* 2000].

Tumor stroma is also the site of interaction between cancer and the immune system. Pancreatic tumors establish a profoundly immunosuppressed microenvironment that is nearly devoid of T lymphocytes. Several stromal cell types harbor immunosuppressive properties, including tumor associated macrophages (TAMs), cancer associated fibroblasts (CAFs), regulatory T cells (T_{reg}) and myeloid derived suppressor cells. Recently, two groups identified a K-ras dependent signal that promotes immunosuppression. Following activation, the principle upregulated cytokine is granulocyte-macrophage colony-stimulating factor (GM-CSF), which was found to promote the recruitment and activation of immature myeloid progenitor cells to become myeloid derived suppressor cells [Bayne *et al.* 2012; Pylayeva-Gupta *et al.* 2012]. Undoubtedly, other such signals exist and should be explored in the coming years.

Future therapeutic options

The many complexities of pancreatic tumors have, to date, overwhelmed our best clinical efforts. However, the investments of the past 30 years in establishing a fundamental understanding of the disease uncovered a number of important and promising leads for new therapeutic approaches. At the most basic level, improved patient management and the advent of multidisciplinary centers specializing in the care of pancreatic cancer patients is improving the quality of life of our patients. High volume centers clearly have improved surgical outcomes [Lieberman *et al.* 1995; Birkmeyer *et al.* 2002] and similar expertise in the endoscopy suite is likely to also improve patient care. Indeed, a recent report described the diagnostic and financial advantages of direct histological processing of fine needle aspiration (FNA) samples rather than use of cytology [Brais *et al.* 2012]. The recent introduction of endoscopic core biopsy needles has also improved the ability to acquire samples for both diagnostic and experimental purposes.

Several promising techniques are under development that may improve diagnostic imaging. Advanced MRI sequences such as diffusion weighted imaging (DWI) and dynamic contrast enhanced (DCE) MRI capitalize on the altered perfusion of pancreatic tumor to provide functional contrast relative to normal or inflamed pancreatic tissue [Fattahi *et al.* 2009; Bali *et al.* 2011; Hur *et al.* 2012; Wiggermann *et al.* 2012; Yao *et al.* 2012]. Advanced endoscopic ultrasound techniques such as contrast ultrasound (which measure tissue perfusion) and ultrasound elastography (which measures tissue stiffness) have shown initial promise as diagnostic and prognostic indicators [Sofuni *et al.* 2005; Sakamoto *et al.* 2008; D'Onofrio *et al.* 2009]. A number of efforts are under way to identify targeted contrast agents that discriminate early cancer or late-stage premalignancies. Among the most promising is a peptide that recognizes extracellular expression of Plectin-1, which was identified initially through a phage-display screen in genetically engineered mouse models of pancreatic cancer [Kelly *et al.* 2008; Bausch *et al.* 2009]. This probe appears to be upregulated in carcinomas *in situ* (PanIN 3) and is being developed for clinical trials as a single photon emission computed tomography (SPECT) probe.

For patients with advanced or metastatic PDA, a number of new therapeutic avenues are being explored. A variety of approaches have been taken to target components of the pancreatic tumor

stroma. PEGPH20, a modified enzyme that breaks down hyaluronan crosslinks in the extracellular matrix, has been shown by two groups to facilitate the delivery of drugs to pancreatic tumors in genetically engineered mice and increase their overall survival [Jacobetz *et al.* 2013; Provenzano *et al.* 2012]. A phase Ib/II clinical trial of PEGPH20 in combination with gemcitabine is now active at multiple sites. Two agents are in clinical trials that take advantage of the paucity of vasculature in pancreatic cancer. The gamma secretase inhibitor RO4929097 (Hoffman La Roche) is being evaluated in previously treated metastatic pancreatic cancer patients in a phase II study. Gamma-secretase is required for activation of Notch pathway signaling, which plays a role in pancreatic tumor angiogenesis. In a genetically engineered mouse model, inhibition of γ -secretase reduced vascularity to critically low levels within the tumor, resulting in cavitating necrosis and increased overall survival when combined with gemcitabine [Cook *et al.* 2012]. A second approach utilizes the presence of hypoxia to activate a chemotherapeutic prodrug. TH-302 is a potent DNA alkylator that is selectively activated in regions of hypoxia and is now undergoing clinical evaluation in combination with gemcitabine. Unfortunately, inhibition of the Hedgehog pathway, one of the earliest stroma targeting strategies, has so far failed to meet expectations. Two different targeted inhibitors of the Smoothened protein, IPI-926 (Saridegib, Infinity Pharmaceuticals) and GDC-0449 (Vismodegib, Genentech) were evaluated in phase II clinical trials, with negative results reported for IPI-926. Investigations are ongoing to understand this disconnect between preclinical and clinical results for these agents. On a positive note, a phase III study of gemcitabine plus Abraxane, a nanoparticle reformulation of taxol, was recently found to have met the primary endpoint, after an encouraging phase II study in which metastatic patients lived an average of 12.2 months [von Hoff *et al.* 2011]. One proposed mechanism of action is the targeting of SPARC, an extracellular matrix protein that is upregulated in the stroma of pancreatic tumors [Desai *et al.* 2009]. However, a recent analysis in genetically engineered mice found that Abraxane alters the sensitivity of pancreatic tumors to gemcitabine through downregulation of cytidine deaminase, leading to higher concentrations of dFdCTP in tumors [Frese *et al.* 2012]. In either case, with a toxicity profile that may be more reasonable than FOLFIRINOX, the regimen may prove to be a welcome new tool for the treatment of pancreatic cancer patients.

Finally, two novel immunotherapy approaches are under development in pancreatic cancer. The observation that GM-CSF promotes a paracrine circuit that helps maintain an immunosuppressive microenvironment has led to the proposal that anti-GM-CSF targeted antibodies may be useful in treating patients with pancreatic cancer [Bayne *et al.* 2012; Pylayeva-Gupta *et al.* 2012]. Another approach was reported in a phase I trial of a CD40 agonist in combination with gemcitabine in metastatic PDA patients. CD40 is an immunostimulant, and the combination therapy resulted in partial responses in 19% of patients and stable disease in 52% of patients. Contrary to initial expectations, the regimen relied on a macrophage-based mechanism of action, as revealed in a genetically engineered mouse model [Beatty *et al.* 2011].

Lessons learned

It is important to heed the hard-won lessons of a generation of clinical researchers [Tabernero and Macarulla, 2009]. As our molecular understanding of cancer in general and PDA specifically increases, it will become increasingly useful to obtain more information about the tumors we are treating. Currently many patients are diagnosed with PDA on the basis of imaging characteristics and a fine needle aspiration, which demonstrates adenocarcinoma but provides little additional tissue for further analysis. In many advanced clinical trials, the reason for failure of encouraging agents is never determined and this limits further directions in PDA research. Where therapies are developed and justified on the basis of tumor biology, it is critical to include pretreatment biopsies and, whenever feasible, to obtain additional post-treatment tumor samples to monitor the effect of targeting interventions on tumor histology and biology. Although this can increase trial costs and is an additional burden to patients, many patients believe in the importance of research efforts and are willing to undergo these procedures as a meaningful contribution to this effort. Moreover, in successful trials, correlative studies can provide valuable guidance for future development efforts. Treatment-related biopsies also facilitate the ability to prospectively test biomarkers, an important tool in identifying appropriate agents for advanced clinical trials [Philip *et al.* 2009].

It is also useful to bear in mind the many missed signals: situations where single arm phase I or II trials led to great hope, only to be disappointed by randomized phase III trials. In some cases this

relates to the marked heterogeneity in outcomes among patients with advanced PDA based on other clinical characteristics such as age, pain status, function status and other comorbidities. These factors are complex and difficult to control. One way to address this limitation is to incorporate a control group in phase II trials to provide context to the reported results. Although this will require more patients and will still necessitate large phase III trials of positive agents [Rubinstein *et al.* 2011], it may reduce the number of agents that progress to expensive, large-scale, but ultimately futile phase III studies [Sharma *et al.* 2011].

Consideration must also be given to the caution necessary when utilizing surrogate markers in clinical trials. Particularly in pancreatic cancer, response rate and progression-free survival have often failed to correlate with increased overall survival. Although additional surrogate markers may prove to be beneficial, ultimately well-designed randomized trials with survival or clinical benefit outcomes will remain the gold standard of therapeutic effect.

In addition, it is important to remember that the majority of patients with PDA are elderly and many have poor functional status related to their tumors. These patients may ultimately benefit from different therapies than a younger, fitter population, and they should be represented in clinical trials. We therefore advocate for dedicated trials of less toxic regimens in the setting of performance status 2 patients. Perhaps most importantly, numerous advanced clinical trials have been terminated early and the data from many of these experiences are not publicly available. An effort must be made to make these data available to researchers in a timely fashion to inform future clinical trial design.

In conclusion, while the clinical outcomes for PDA have not improved sufficiently in the last decades, a large wealth of knowledge has been developed and is now being translated towards the ultimate goal of improving treatment outcomes for patients with PDA. We are filled with optimism that these efforts will be successful.

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References

- Abou-Alfa, G., Letourneau, R., Harker, G., Modiano, M., Hurwitz, H., Tchekmedyian, N. *et al.* (2006) Randomized phase III study of exatecan and gemcitabine compared with gemcitabine alone in untreated advanced pancreatic cancer. *J Clin Oncol* 24: 4441–4447.
- Achiwa, H., Oguri, T., Sato, S., Maeda, H., Niimi, T. and Ueda, R. (2004) Determinants of sensitivity and resistance to gemcitabine: the roles of human equilibrative nucleoside transporter 1 and deoxycytidine kinase in non-small cell lung cancer. *Cancer Sci* 95: 753–757.
- Allison, D., Piantadosi, S., Hruban, R., Dooley, W., Fishman, E., Yeo, C. *et al.* (1998) DNA content and other factors associated with ten-year survival after resection of pancreatic carcinoma. *J Surg Oncol* 67: 151–159.
- Almoguera, C., Shibata, D., Forrester, K., Martin, J., Arnheim, N. and Perucho, M. (1988) Most human carcinomas of the exocrine pancreas contain mutant C-K-Ras genes. *Cell* 53: 549–554.
- Andre, T., Boni, C., Mounedji-Boudiaf, L., Navarro, M., Tabernero, J., Hickish, T. *et al.* (2004) Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 350: 2343–2351.
- Andre, T., Boni, C., Navarro, M., Tabernero, J., Hickish, T., Topham, C. *et al.* (2009) Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the mosaic trial. *J Clin Oncol* 27: 3109–3116.
- Bailey, J., Swanson, B., Hamada, T., Eggers, J., Singh, P., Caffery, T. *et al.* (2008) Sonic hedgehog promotes desmoplasia in pancreatic cancer. *Clin Cancer Res* 14: 5995–6004.
- Bakkevold, K., Arnesjo, B. and Kambestad, B. (1992) Carcinoma of the pancreas and papilla of Vater: presenting symptoms, signs, and diagnosis related to stage and tumour site. A prospective multicentre trial in 472 patients. Norwegian Pancreatic Cancer Trial. *Scand J Gastroenterol* 27: 317–325.
- Bali, M., Metens, T., Denolin, V., Delhaye, M., Demetter, P., Closset, J. *et al.* (2011) Tumoral and nontumoral pancreas: correlation between quantitative dynamic contrast-enhanced MR imaging and histopathologic parameters. *Radiology* 261: 456–466.
- Bartsch, D., Gress, T. and Langer, P. (2012) Familial pancreatic cancer – current knowledge. *Nat Rev Gastroenterol Hepatol* 9: 445–453.
- Bartsch, D., Kress, R., Sina-Frey, M., Grutzmann, R., Gerdes, B., Pilarsky, C. *et al.* (2004) Prevalence of familial pancreatic cancer in Germany. *Int J Cancer* 110: 902–906.
- Bausch, D., Mino-Kenudson, M., Fernandez-Del Castillo, C., Warshaw, A., Kelly, K. and Thayer, S. (2009) Plectin-1 is a biomarker of malignant pancreatic intraductal papillary mucinous neoplasms. *J Gastrointest Surg* 13: 1948–1954; discussion 1954.
- Bayne, L., Beatty, G., Jhala, N., Clark, C., Rhim, A., Stanger, B. *et al.* (2012) Tumor-derived granulocyte-macrophage colony-stimulating factor regulates myeloid inflammation and T cell immunity in pancreatic cancer. *Cancer Cell* 21: 822–835.
- Beatty, G., Chiorean, E., Fishman, M., Saboury, B., Teitelbaum, U., Sun, W. *et al.* (2011) CD40 agonists alter tumor stroma and show efficacy against pancreatic carcinoma in mice and humans. *Science* 331: 1612–1616.
- Berlin, J., Catalano, P., Thomas, J., Kugler, J., Haller, D. and Benson, A., III. (2002) Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. *J Clin Oncol* 20: 3270–3275.
- Berman, D., Karhadkar, S., Maitra, A., Montes De Oca, R., Gerstenblith, M., Briggs, K. *et al.* (2003) Widespread requirement for hedgehog ligand stimulation in growth of digestive tract tumours. *Nature* 425: 846–851.
- Biankin, A., Waddell, N., Kassahn, K., Gingras, M., Muthuswamy, L., Johns, A. *et al.* (2012) Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. *Nature* 491: 399–405.
- Bilimoria, K., Bentrem, D., Ko, C., Ritchey, J., Stewart, A., Winchester, D. *et al.* (2007) Validation of the 6th edition AJCC Pancreatic Cancer Staging System: report from the National Cancer Database. *Cancer* 110: 738–744.
- Birkmeyer, J., Siewers, A., Finlayson, E., Stukel, T., Lucas, F., Batista, I. *et al.* (2002) Hospital volume and surgical mortality in the United States. *N Engl J Med* 346: 1128–1137.
- Brais, R., Davies, S., O'Donovan, M., Simpson, B., Cook, N., Darbonne, W. *et al.* (2012) Direct histological processing of EUS biopsies enables rapid molecular biomarker analysis for interventional pancreatic cancer trials. *Pancreatol* 12: 8–15.
- Bramhall, S., Rosemurgy, A., Brown, P., Bowry, C. and Buckels, J. (2001) Marimastat as first-line therapy for patients with unresectable pancreatic cancer: a randomized trial. *J Clin Oncol* 19: 3447–3455.
- Burris, H., III, Moore, M., Andersen, J., Green, M., Rothenberg, M., Modiano, M. *et al.*

- (1997) Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 15: 2403–2413.
- Caldas, C., Hahn, S., Da Costa, L., Redston, M., Schutte, M., Seymour, A. *et al.* (1994) Frequent somatic mutations and homozygous deletions of the P16 (Mts1) gene in pancreatic adenocarcinoma. *Nat Genet* 8: 27–32.
- Canto, M., Hruban, R., Fishman, E., Kamel, I., Schulick, R., Zhang, Z. *et al.* (2012) Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. *Gastroenterology* 142: 796–804; quiz e714–795.
- Chari, S., Leibson, C., Rabe, K., Ransom, J., De Andrade, M. and Petersen, G. (2005) Probability of pancreatic cancer following diabetes: a population-based study. *Gastroenterology* 129: 504–511.
- Chu, G., Kimmelman, A., Hezel, A. and Depinho, R. (2007) Stromal biology of pancreatic cancer. *J Cell Biochem* 101: 887–907.
- Ciccolini, J., Dahan, L., Andre, N., Evrard, A., Duluc, M., Blesius, A. *et al.* (2010) Cytidine deaminase residual activity in serum is a predictive marker of early severe toxicities in adults after gemcitabine-based chemotherapies. *J Clin Oncol* 28: 160–165.
- Collins, M., Bednar, F., Zhang, Y., Brisset, J., Galban, S., Galban, C. *et al.* (2012) Oncogenic Kras is required for both the initiation and maintenance of pancreatic cancer in mice. *J Clin Invest* 122: 639–653.
- Colucci, G., Labianca, R., Di Costanzo, F., Gebbia, V., Carteni, G., Massidda, B. *et al.* (2010) Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 Study. *J Clin Oncol* 28: 1645–1651.
- Conroy, T., Desseigne, F., Ychou, M., Bouche, O., Guimbaud, R., Becouarn, Y. *et al.* (2011) FOLFIRINOX *versus* gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 364: 1817–1825.
- Cook, N., Frese, K., Bapiro, T., Jacobetz, M., Gopinathan, A., Miller, J. *et al.* (2012) Gamma secretase inhibition promotes hypoxic necrosis in mouse pancreatic ductal adenocarcinoma. *J Exp Med* 209: 437–444.
- Cunningham, D., Chau, I., Stocken, D., Valle, J., Smith, D., Steward, W. *et al.* (2009) Phase III randomized comparison of gemcitabine *versus* gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol* 27: 5513–5518.
- Desai, N., Trieu, V., Damascelli, B. and Soon-Shiong, P. (2009) SPARC expression correlates with tumor response to albumin-bound paclitaxel in head and neck cancer patients. *Transl Oncol* 2: 59–64.
- D'Onofrio, M., Zamboni, G., Malago, R., Mantovani, W., Principe, F., Gallotti, A. *et al.* (2009) Resectable pancreatic adenocarcinoma: is the enhancement pattern at contrast-enhanced ultrasonography a pre-operative prognostic factor? *Ultrasound Med Biol* 35: 1929–1937.
- Douillard, J., Rosell, R., De Lena, M., Carpagnano, F., Ramlau, R., Gonzales-Larriba, J. *et al.* (2006) Adjuvant vinorelbine plus cisplatin *versus* observation in patients with completely resected stage Ib–IIa non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [Anita]): a randomised controlled trial. *Lancet Oncol* 7: 719–727.
- Eliopoulos, N., Cournoyer, D. and Momparler, R. (1998) Drug resistance to 5-aza-2'-deoxycytidine, 2',2'-difluorodeoxycytidine, and cytosine arabinoside conferred by retroviral-mediated transfer of human cytidine deaminase cDNA into murine cells. *Cancer Chemother Pharmacol* 42: 373–378.
- Erkan, M., Hausmann, S., Michalski, C., Fingerle, A., Dobritz, M., Kleeff, J. *et al.* (2012) The Role of stroma in pancreatic cancer: diagnostic and therapeutic implications. *Nat Rev Gastroenterol Hepatol* 9: 454–467.
- Farrell, J., Bae, K., Wong, J., Guha, C., Dicker, A. and Elsaleh, H. (2012) Cytidine deaminase single-nucleotide polymorphism is predictive of toxicity from gemcitabine in patients with pancreatic cancer: RTOG 9704. *Pharmacogenomics J* 12: 395–403.
- Farnell, M., Pearson, R., Sarr, M., Dimagno, E., Burgart, L., Dahl, T. *et al.* (2005) A Prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. *Surgery* 138: 618–628; discussion 628–630.
- Farrell, J., Elsaleh, H., Garcia, M., Lai, R., Ammar, A., Regine, W. *et al.* (2009) Human equilibrative nucleoside transporter 1 levels predict response to gemcitabine in patients with pancreatic cancer. *Gastroenterology* 136: 187–195.
- Fattahi, R., Balci, N., Perman, W., Hsueh, E., Alkaade, S., Havlioglu, N. *et al.* (2009) Pancreatic diffusion-weighted imaging (DWI): comparison between mass-forming focal pancreatitis (FP), pancreatic cancer (PC), and normal pancreas. *J Magn Reson Imaging* 29: 350–356.
- Ferrone, C., Pieretti-Vanmarcke, R., Bloom, J., Zheng, H., Szymonifka, J., Wargo, J. *et al.* (2012) Pancreatic ductal adenocarcinoma: long-term survival does not equal cure. *Surgery* 152(Suppl.): S43–S49.

- Frebourg, T., Bercoff, E., Manchon, N., Senant, J., Basuyau, J., Breton, P. *et al.* (1988) The evaluation of Ca 19-9 antigen level in the early detection of pancreatic cancer. A prospective study of 866 patients. *Cancer* 62: 2287–2290.
- Frese, K., Neesse, A., Cook, N., Bapiro, T., Lolkema, M., Jodrell, D. *et al.* (2012) nab-Paclitaxel potentiates gemcitabine activity by reducing cytidine deaminase levels in a mouse model of pancreatic cancer. *Cancer Discov* 2: 260–269.
- Fusaroli, P., Spada, A., Mancino, M. and Caletti, G. (2010) Contrast harmonic echo-endoscopic ultrasound improves accuracy in diagnosis of solid pancreatic masses. *Clin Gastroenterol Hepatol* 8: 629–634, e621–622.
- Giovannetti, E., Tibaldi, C., Falcone, A., Danesi, R. and Peters, G. (2010) Impact of cytidine deaminase polymorphisms on toxicity after gemcitabine: the question is still ongoing. *J Clin Oncol* 28: e221–222; author reply e223–225.
- Goggins, M. (2005) Molecular markers of early pancreatic cancer. *J Clin Oncol* 23: 4524–4531.
- Goncalves, A., Gilibert, M., Francois, E., Dahan, L., Perrier, H., Lamy, R. *et al.* (2012) Baypan Study: a double-blind phase III randomized trial comparing gemcitabine plus sorafenib and gemcitabine plus placebo in patients with advanced pancreatic cancer. *Ann Oncol* 23: 2799–2805.
- Haeno, H., Gonen, M., Davis, M., Herman, J., Iacobuzio-Donahue, C. and Michor, F. (2012) Computational modeling of pancreatic cancer reveals kinetics of metastasis suggesting optimum treatment strategies. *Cell* 148: 362–375.
- Hahn, S., Hoque, A., Moskaluk, C., Da Costa, L., Schutte, M., Rozenblum, E. *et al.* (1996a) Homozygous deletion map at 18q21.1 in pancreatic cancer. *Cancer Res* 56: 490–494.
- Hahn, S., Schutte, M., Hoque, A., Moskaluk, C., Da Costa, L., Rozenblum, E. *et al.* (1996b) DPC4, a candidate tumor suppressor gene at human chromosome 18q21.1. *Science* 271: 350–353.
- Hansel, D., Kern, S. and Hruban, R. (2003) Molecular Pathogenesis of pancreatic cancer. *Annu Rev Genomics Hum Genet* 4: 237–256.
- Harrison, L., Chadha, M., Hill, R., Hu, K. and Shasha, D. (2002) Impact of tumor hypoxia and anemia on radiation therapy outcomes. *Oncologist* 7: 492–508.
- Heinemann, V., Hertel, L., Grindey, G. and Plunkett, W. (1988) Comparison of the cellular pharmacokinetics and toxicity of 2',2'-difluorodeoxycytidine and 1-beta-D-arabinofuranosylcytosine. *Cancer Res* 48: 4024–4031.
- Heinemann, V., Quietzs, D., Gieseler, F., Gonnermann, M., Schonekas, H., Rost, A. *et al.* (2006) Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol* 24: 3946–3952.
- Heinemann, V., Vehling-Kaiser, U., Waldschmidt, D., Kettner, E., Marten, A., Winkelmann, C. *et al.* (2012) Gemcitabine plus erlotinib followed by capecitabine *versus* capecitabine plus erlotinib followed by gemcitabine in advanced pancreatic cancer: final results of a randomised phase III trial of the 'Arbeitsgemeinschaft Internistische Onkologie' (AIO-PK0104). *Gut*, in press. DOI: 10.1136/gutjnl-2012-302759.
- Heinen, M., Verhage, B., Goldbohm, R. and Van Den Brandt, P. (2010) Active and passive smoking and the risk of pancreatic cancer in the Netherlands Cohort Study. *Cancer Epidemiol Biomarkers Prev* 19: 1612–1622.
- Herrmann, R., Bodoky, G., Ruhstaller, T., Glimelius, B., Bajetta, E., Schuller, J. *et al.* (2007) Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. *J Clin Oncol* 25: 2212–2217.
- Hezel, A., Kimmelman, A., Stanger, B., Bardeesy, N. and Depinho, R. (2006) Genetics and Biology of pancreatic ductal adenocarcinoma. *Genes Dev* 20: 1218–1249.
- Holzappel, K., Reiser-Erkan, C., Fingerle, A., Erkan, M., Eiber, M., Rummeny, E. *et al.* (2011) Comparison of diffusion-weighted MR imaging and multidetector-row CT in the detection of liver metastases in patients operated for pancreatic cancer. *Abdom Imaging* 36: 179–184.
- Hruban, R., Canto, M., Goggins, M., Schulick, R. and Klein, A. (2010) Update on familial pancreatic cancer. *Adv Surg* 44: 293–311.
- Hruban, R., Petersen, G., Goggins, M., Tersmette, A., Offerhaus, G., Falatko, F. *et al.* (1999) Familial pancreatic cancer. *Ann Oncol* 10(Suppl. 4): 69–73.
- Hur, B., Lee, J., Lee, J., Park, J., Kim, S., Joo, I. *et al.* (2012) Magnetic resonance imaging findings of the mass-forming type of autoimmune pancreatitis: comparison with pancreatic adenocarcinoma. *J Magn Reson Imaging* 36: 188–197.
- Iodice, S., Gandini, S., Maisonneuve, P. and Lowenfels, A. (2008) Tobacco and the risk of pancreatic cancer: a review and meta-analysis. *Langenbecks Arch Surg* 393: 535–545.
- Jacobetz, M., Chan, D., Neesse, A., Bapiro, T., Cook, N., Frese, K. *et al.* (2013) Hyaluronan impairs

- vascular function and drug delivery in a mouse model of pancreatic cancer. *Gut* 62: 112–120.
- Jemal, A., Bray, F., Center, M., Ferlay, J., Ward, E. and Forman, D. (2011) Global cancer statistics. *CA Cancer J Clin* 61: 69–90.
- Jones, S., Zhang, X., Parsons, D., Lin, J., Leary, R., Angenendt, P. *et al.* (2008) Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. *Science* 321: 1801–1806.
- Kelly, K., Bardeesy, N., Anbazhagan, R., Gurumurthy, S., Berger, J., Alencar, H. *et al.* (2008) Targeted nanoparticles for imaging incipient pancreatic ductal adenocarcinoma. *PLoS Med* 5: e85.
- Kelsen, D., Portenoy, R., Thaler, H., Niedzwiecki, D., Passik, S., Tao, Y. *et al.* (1995) Pain and depression in patients with newly diagnosed pancreas cancer. *J Clin Oncol* 13: 748–755.
- Khorana, A. and Fine, R. (2004) Pancreatic cancer and thromboembolic disease. *Lancet Oncol* 5: 655–663.
- Kindler, H., Ioka, T., Richel, D., Bennisouna, J., Letourneau, R., Okusaka, T. *et al.* (2011) Axitinib plus gemcitabine *versus* placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase III study. *Lancet Oncol* 12: 256–262.
- Kindler, H., Niedzwiecki, D., Hollis, D., Sutherland, S., Schrag, D., Hurwitz, H. *et al.* (2010) Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). *J Clin Oncol* 28: 3617–3622.
- Klein, A., Brune, K., Petersen, G., Goggins, M., Tersmette, A., Offerhaus, G. *et al.* (2004) Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. *Cancer Res* 64: 2634–2638.
- Klinkenbijn, J., Jeekel, J., Sahmoud, T., van Pel, R., Couvreur, M., Veenhof, C. *et al.* (1999) Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periaampullary region: phase III TRIAL of the EORTC Gastrointestinal Tract Cancer Cooperative Group. *Ann Surg* 230: 776–782; discussion 782–774.
- Komar, G., Kauhanen, S., Liukko, K., Seppanen, M., Kajander, S., Ovaska, J. *et al.* (2009) Decreased blood flow with increased metabolic activity: a novel sign of pancreatic tumor aggressiveness. *Clin Cancer Res* 15: 5511–5517.
- Koong, A., Mehta, V., Le, Q., Fisher, G., Terris, D., Brown, J. *et al.* (2000) Pancreatic tumors show high levels of hypoxia. *Int J Radiat Oncol Biol Phys* 48: 919–922.
- Langer, P., Kann, P., Fendrich, V., Habbe, N., Schneider, M., Sina, M. *et al.* (2009) Five years of prospective screening of high-risk individuals from families with familial pancreatic cancer. *Gut* 58: 1410–1418.
- Lieberman, M., Kilburn, H., Lindsey, M. and Brennan, M. (1995) Relation of perioperative deaths to hospital volume among patients undergoing pancreatic resection for malignancy. *Ann Surg* 222: 638–645.
- Louvet, C., Labianca, R., Hammel, P., Lledo, G., Zampino, M., Andre, T. *et al.* (2005) Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a gercor and giscad phase III trial. *J Clin Oncol* 23: 3509–3516.
- Mackey, J., Mani, R., Selner, M., Mowles, D., Young, J., Belt, J. *et al.* (1998) Functional nucleoside transporters are required for gemcitabine influx and manifestation of toxicity in cancer cell lines. *Cancer Res* 58: 4349–4357.
- Maitra, A. and Hruban, R. (2008) Pancreatic cancer. *Annu Rev Pathol* 3: 157–188.
- Marechal, R., Bachet, J., Mackey, J., Dalban, C., Demetter, P., Graham, K. *et al.* (2012) Levels of gemcitabine transport and metabolism proteins predict survival times of patients treated with gemcitabine for pancreatic adenocarcinoma. *Gastroenterology* 143: 664–674 e661–666.
- Matsubara, H., Itoh, A., Kawashima, H., Kasugai, T., Ohno, E., Ishikawa, T. *et al.* (2011) Dynamic quantitative evaluation of contrast-enhanced endoscopic ultrasonography in the diagnosis of pancreatic diseases. *Pancreas* 40: 1073–1079.
- Mini, E., Nobili, S., Caciagli, B., Landini, I. and Mazzei, T. (2006) Cellular pharmacology of gemcitabine. *Ann Oncol* 17(Suppl. 5): v7–12.
- Moore, M., Goldstein, D., Hamm, J., Figer, A., Hecht, J., Gallinger, S. *et al.* (2007) Erlotinib Plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 25: 1960–1966.
- Moore, M., Hamm, J., Dancy, J., Eisenberg, P., Dagenais, M., Fields, A. *et al.* (2003) Comparison of gemcitabine *versus* the matrix metalloproteinase inhibitor BAY 12-9566 in patients with advanced or metastatic adenocarcinoma of the pancreas: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 21: 3296–3302.
- Morton, J., Timpson, P., Karim, S., Ridgway, R., Athineos, D., Doyle, B. *et al.* (2010) Mutant P53 drives metastasis and overcomes growth arrest/

- senescence in pancreatic cancer. *Proc Natl Acad Sci U S A* 107: 246–251.
- Neesse, A., Michl, P., Frese, K., Feig, C., Cook, N., Jacobetz, M. *et al.* (2011) Stromal biology and therapy in pancreatic cancer. *Gut* 60: 861–868.
- Neoptolemos, J., Stocken, D., Bassi, C., Ghaneh, P., Cunningham, D., Goldstein, D. *et al.* (2010) Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA* 304: 1073–1081.
- Neoptolemos, J., Stocken, D., Friess, H., Bassi, C., Dunn, J., Hickey, H. *et al.* (2004) A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 350: 1200–1210.
- Nolan-Stevaux, O., Lau, J., Truitt, M., Chu, G., Hebrok, M., Fernandez-Zapico, M. *et al.* (2009) Gli1 is regulated through smoothened-independent mechanisms in neoplastic pancreatic ducts and mediates pdac cell survival and transformation. *Genes Dev* 23: 24–36.
- Oettle, H., Post, S., Neuhaus, P., Gellert, K., Langrehr, J., Ridwelski, K. *et al.* (2007) Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled Trial. *JAMA* 297: 267–277.
- Oettle, H., Richards, D., Ramanathan, R., van Laethem, J., Peeters, M., Fuchs, M. *et al.* (2005) A phase III trial of pemetrexed plus gemcitabine versus gemcitabine in patients with unresectable or metastatic pancreatic cancer. *Ann Oncol* 16: 1639–1645.
- Oguri, T., Achiwa, H., Muramatsu, H., Ozasa, H., Sato, S., Shimizu, S. *et al.* (2007) The absence of human equilibrative nucleoside transporter 1 expression predicts nonresponse to gemcitabine-containing chemotherapy in non-small cell lung cancer. *Cancer Lett* 256: 112–119.
- Olive, K., Jacobetz, M., Davidson, C., Gopinathan, A., McIntyre, D., Honess, D. *et al.* (2009) Inhibition of hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. *Science* 324: 1457–1461.
- Olive, K., Tuveson, D., Ruhe, Z., Yin, B., Willis, N., Bronson, R.T. *et al.* (2004) Mutant p53 gain of function in two mouse models of Li-Fraumeni syndrome. *Cell* 119: 847–860.
- Pausch, T., Hartwig, W., Hinz, U., Swolana, T., Bundy, B., Hackert, T. *et al.* (2012) Cachexia but not obesity worsens the postoperative outcome after pancreatoduodenectomy in pancreatic cancer. *Surgery* 152: S81–88.
- Pellegata, N., Sessa, F., Renault, B., Bonato, M., Leone, B., Solcia, E. *et al.* (1994) K-ras and p53 gene mutations in pancreatic cancer: ductal and nonductal tumors progress through different genetic lesions. *Cancer Res* 54: 1556–1560.
- Perez-Mancera, P., Rust, A., van der Weyden, L., Kristiansen, G., Li, A., Sarver, A. *et al.* (2012) The deubiquitinase USP9X suppresses pancreatic ductal adenocarcinoma. *Nature* 486: 266–270.
- Philip, P., Benedetti, J., Corless, C., Wong, R., O'Reilly, E., Flynn, P. *et al.* (2010) Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-Directed Intergroup Trial S0205. *J Clin Oncol* 28: 3605–3610.
- Philip, P., Mooney, M., Jaffe, D., Eckhardt, G., Moore, M., Meropol, N. *et al.* (2009) Consensus report of the national cancer institute clinical trials planning meeting on pancreas cancer treatment. *J Clin Oncol* 27: 5660–5669.
- Poplin, E., Feng, Y., Berlin, J., Rothenberg, M., Hochster, H., Mitchell, E. *et al.* (2009) Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 27: 3778–3785.
- Porta, M., Fabregat, X., Malats, N., Guarnier, L., Carrato, A., De Miguel, A. *et al.* (2005) Exocrine pancreatic cancer: symptoms at presentation and their relation to tumour site and stage. *Clin Transl Oncol* 7: 189–197.
- Provenzano, P., Cuevas, C., Chang, A., Goel, V., von Hoff, D. and Hingorani, S.R. (2012) Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. *Cancer Cell* 21: 418–429.
- Pylayeva-Gupta, Y., Lee, K., Hajdu, C., Miller, G. and Bar-Sagi, D. (2012) Oncogenic Kras-induced GM-CSF production promotes the development of pancreatic neoplasia. *Cancer Cell* 21: 836–847.
- Raimondi, S., Maisonneuve, P. and Lowenfels, A.B. (2009) Epidemiology of pancreatic cancer: an overview. *Nat Rev Gastroenterol Hepatol* 6: 699–708.
- Redston, M., Caldas, C., Seymour, A., Hruban, R., Da Costa, L., Yeo, C. *et al.* (1994) P53 mutations in pancreatic carcinoma and evidence of common involvement of homocopolymer tracts in DNA microdeletions. *Cancer Res* 54: 3025–3033.
- Regine, W., Winter, K., Abrams, R., Safran, H., Hoffman, J., Konski, A. *et al.* (2008) Fluorouracil vs gemcitabine chemotherapy before and after

- fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. *JAMA* 299: 1019–1026.
- Regine, W., Winter, K., Abrams, R., Safran, H., Hoffman, J., Konski, A. *et al.* (2011) Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/RTOG 9704 phase III trial. *Ann Surg Oncol* 18: 1319–1326.
- Rhim, A., Mirek, E., Aiello, N., Maitra, A., Bailey, J., Mcallister, F. *et al.* (2012) EMT and dissemination precede pancreatic tumor formation. *Cell* 148: 349–361.
- Rocha Lima, C., Green, M., Rotche, R., Miller, W., Jr, Jeffrey, G., Cisar, L. *et al.* (2004) Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol* 22: 3776–3783.
- Rubinstein, L., Leblanc, M. and Smith, M. (2011) More randomization in phase II trials: necessary but not sufficient. *J Natl Cancer Inst* 103: 1075–1077.
- Saftoiu, A., Dietrich, C. and Vilmann, P. (2012) Contrast-enhanced harmonicendoscopic ultrasound. *Endoscopy* 44: 612–617.
- Sakamoto, H., Kitano, M., Suetomi, Y., Maekawa, K., Takeyama, Y. and Kudo, M. (2008) Utility of contrast-enhanced endoscopic ultrasonography for diagnosis of small pancreatic carcinomas. *Ultrasound Med Biol* 34: 525–532.
- Schutte, M., Hruban, R., Geradts, J., Maynard, R., Hilgers, W., Rabindran, S. *et al.* (1997) Abrogation of the Rb/p16 tumor-suppressive pathway in virtually all pancreatic carcinomas. *Cancer Res* 57: 3126–3130.
- Shaib, Y., Davila, J. and El-Serag, H. (2006) The epidemiology of pancreatic cancer in the United States: changes below the surface. *Aliment Pharmacol Ther* 24: 87–94.
- Sharma, M., Stadler, W. and Ratain, M. (2011) Randomized phase II trials: a long-term investment with promising returns. *J Natl Cancer Inst* 103: 1093–1100.
- Shi, C., Hruban, R. and Klein, A. (2009) Familial pancreatic cancer. *Arch Pathol Lab Med* 133: 365–374.
- Siegel, R., Naishadham, D. and Jemal, A. (2012) Cancer statistics, 2012. *CA Cancer J Clin* 62: 10–29.
- Sofuni, A., Iijima, H., Moriyasu, F., Nakayama, D., Shimizu, M., Nakamura, K. *et al.* (2005) Differential diagnosis of pancreatic tumors using ultrasound contrast imaging. *J Gastroenterol* 40: 518–525.
- Sparano, J., Wang, M., Martino, S., Jones, V., Perez, E., Saphner, T. *et al.* (2008) Weekly paclitaxel in the adjuvant treatment of breast cancer. *N Engl J Med* 358: 1663–1671.
- Stathis, A. and Moore, M. (2010) Advanced pancreatic carcinoma: current treatment and future challenges. *Nat Rev Clin Oncol* 7: 163–172.
- Steinberg, W. (1990) The clinical utility of the CA 19-9 tumor-associated antigen. *Am J Gastroenterol* 85: 350–355.
- Stocken, D., Buchler, M., Dervenis, C., Bassi, C., Jeekel, H., Klinkenbijn, J. *et al.* (2005) Meta-analysis of randomised adjuvant therapy trials for pancreatic cancer. *Br J Cancer* 92: 1372–1381.
- Sugiyama, E., Kaniwa, N., Kim, S., Kikura-Hanajiri, R., Hasegawa, R., Maekawa, K. *et al.* (2007) Pharmacokinetics of gemcitabine in Japanese cancer patients: the impact of a cytidine deaminase polymorphism. *J Clin Oncol* 25: 32–42.
- Tabernero, J. and Macarulla, T. (2009) Changing the paradigm in conducting randomized clinical studies in advanced pancreatic cancer: an opportunity for better clinical development. *J Clin Oncol* 27: 5487–5491.
- Tan, X., Reid Lombardo, K., Bamlet, W., Oberg, A., Robinson, D., Anderson, K. *et al.* (2011) Aspirin, nonsteroidal anti-inflammatory drugs, acetaminophen, and pancreatic cancer risk: a clinic-based case-control study. *Cancer Prev Res* 4: 1835–1841.
- Tanaka, M., Javle, M., Dong, X., Eng, C., Abbruzzese, J. and Li, D. (2010) Gemcitabine metabolic and transporter gene polymorphisms are associated with drug toxicity and efficacy in patients with locally advanced pancreatic cancer. *Cancer* 116: 5325–5335.
- Thiebaut, A., Jiao, L., Silverman, D., Cross, A., Thompson, F., Subar, A. *et al.* (2009) Dietary fatty acids and pancreatic cancer in the NIH-AARP Diet and Health Study. *J Natl Cancer Inst* 101: 1001–1011.
- Tian, H., Callahan, C., Dupree, K., Darbonne, W., Ahn, C., Scales, S. *et al.* (2009) Hedgehog signaling is restricted to the stromal compartment during pancreatic carcinogenesis. *Proc Natl Acad Sci U S A* 106: 4254–4259.
- Tibaldi, C., Giovannetti, E., Vasile, E., Mey, V., Laan, A., Nannizzi, S. *et al.* (2008) Correlation of CDA, ERCC1, and XPD polymorphisms with response and survival in gemcitabine/cisplatin-treated advanced non-small cell lung cancer patients. *Clin Cancer Res* 14: 1797–1803.
- Van Cutsem, E., van de Velde, H., Karasek, P., Oettle, H., Vervenne, W., Szawlowski, A. *et al.* (2004) Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. *J Clin Oncol* 22: 1430–1438.

- Van Cutsem, E., Vervenne, W., Bennouna, J., Humblet, Y., Gill, S., van Laethem, J. *et al.* (2009) Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. *J Clin Oncol* 27: 2231–2237.
- Verna, E., Hwang, C., Stevens, P., Rotterdam, H., Stavropoulos, S., Sy, C. *et al.* (2010) Pancreatic cancer screening in a prospective cohort of high-risk patients: a comprehensive strategy of imaging and genetics. *Clin Cancer Res* 16: 5028–5037.
- Von Hoff, D., Ramanathan, R., Borad, M., Laheru, D., Smith, L., Wood, T. *et al.* (2011) Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. *J Clin Oncol* 29: 4548–4554.
- Wiggermann, P., Grutzmann, R., Weissenbock, A., Kamusella, P., Dittert, D. and Stroszczynski, C. (2012) Apparent diffusion coefficient measurements of the pancreas, pancreas carcinoma, and mass-forming focal pancreatitis. *Acta Radiol* 53: 135–139.
- Winter, J., Brennan, M., Tang, L., D'Angelica, M., Dematteo, R., Fong, Y. *et al.* (2012) Survival after resection of pancreatic adenocarcinoma: results from a single institution over three decades. *Ann Surg Oncol* 19: 169–175.
- Yachida, S., Jones, S., Bozic, I., Antal, T., Leary, R., Fu, B. *et al.* (2010) Distant metastasis occurs late during the genetic evolution of pancreatic cancer. *Nature* 467: 1114–1117.
- Yachida, S., White, C., Naito, Y., Zhong, Y., Brosnan, J., Macgregor-Das, A. *et al.* (2012) Clinical significance of the genetic landscape of pancreatic cancer and implications for identification of potential long term survivors. *Clin Cancer Res* 18: 6339–6347.
- Yao, X., Zeng, M., Wang, H., Sun, F., Rao, S. and Ji, Y. (2012) Evaluation of pancreatic cancer by multiple breath-hold dynamic contrast-enhanced magnetic resonance imaging at 3.0T. *Eur J Radiol* 81: e917–922.
- Ying, H., Kimmelman, A., Lyssiotis, C., Hua, S., Chu, G., Fletcher-Sananikone, E. *et al.* (2012) Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism. *Cell* 149: 656–670.

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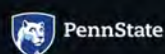
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Appendix OH02

Pilot study of irinotecan/oxaliplatin (IROX) combination chemotherapy for patients with gemcitabine- and 5-fluorouracil- refractory pancreatic cancer

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Summary Background Gemcitabine- and 5-fluorouracil (5-FU)- based chemotherapy is a commonly used adjuvant or palliative treatment for patients with pancreatic cancer. However, a standard chemotherapy regimen has yet to be developed for patients refractory to gemcitabine and 5-FU treatment. We attempted to evaluate the efficacy and safety of a combination of irinotecan and oxaliplatin (IROX) as a

salvage treatment for patients with gemcitabine- and 5-FU-refractory pancreatic cancer. *Patients and Methods* Patients with advanced pancreatic cancer who were refractory to prior gemcitabine- and 5-FU- based chemotherapy were enrolled in this study. IROX chemotherapy was administered as follows: Irinotecan, 150 mg/m² on day 1; and oxaliplatin, 85 mg/m² on day 1 over 90 min every 2 weeks. *Result* From Mar. 2006 to Dec. 2008, a total of 14 patients were administered 50 cycles of chemotherapy. The male-to-female ratio of the patient group was 11:3. These patients ranged in age from 48 to 73 years (median 65.5 years old). 3 patients (21.4%) evidenced partial response. four patients (28.6%) exhibited stable disease. The median time to progression and overall survival time were 1.4 (95% CI: 1.2–1.6) months and 4.1 (95% CI: 2.0–6.2) months, respectively. Major hematologic toxicities included grade 1–2 anemia (88%), neutropenia (36%), thrombocytopenia (30%), and grade 3–4 neutropenia (10%). The most frequently detected non-hematological toxicities were grade 3 diarrhea (14%). *Conclusion* The IROX regimen appears to constitute a feasible and tolerable salvage therapy in patients with advanced pancreatic cancer who have been previously treated with gemcitabine- and 5-FU-based chemotherapy.

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Introduction

The role of chemotherapy in pancreatic cancer patients has been the subject of a great deal of controversy. Gemcitabine

has been extensively utilized as a standard first-line chemotherapy agent in cases of advanced pancreatic cancer [1]. Recent large randomized phase III trials in cases of advanced pancreatic cancer have shown that the addition of capecitabine or erlotinib to gemcitabine yield results superior to those noted with single-agent gemcitabine treatment [2, 3]. Despite several efforts, the efficacy of gemcitabine on the course of the disease has proven marginal, as was also the case with the progress of advanced pancreatic cancer within 4 months after gemcitabine-based first-line chemotherapy [4, 5]. Additionally, patients with advanced pancreatic cancer have been shown to have a 5-year survival rate of less than 5% [5, 6].

Prior to the appearance of gemcitabine, 5-fluorouracil was the drug most frequently utilized for the treatment of advanced pancreatic cancer. 5-fluorouracil-based multi-drug combination regimens have been reported previously to confer a survival advantage over best supportive care in cases of advanced pancreatic cancer [7]. Furthermore, the treatment of advanced pancreatic cancer patients after failure with first-line chemotherapy remains controversial. Owing to poor performance status and rapid clinical deterioration, approximately half of advanced pancreatic cancer patients who evidence progression after gemcitabine-based chemotherapy are ineligible for second-line chemotherapy. Therefore, only a limited number of studies have addressed the role of second-line chemotherapy in cases of advanced pancreatic cancer.

Irinotecan (CPT-11) is a semisynthetic, watersoluble derivative of the plant alkaloid camptothecin. After conversion to its active metabolite, SN-38, irinotecan functions by inhibiting DNA topoisomerase I, thereby interfering with DNA replication and cell division [8]. The results of an irinotecan-containing regimen in the treatment of gastrointestinal cancers have been relatively encouraging [9, 10]. Irinotecan is also highly active on pancreatic tumor cells in culture, and also in xenograft models [11]. Irinotecan monotherapy has been previously tested in patients with previously untreated advanced pancreatic cancer [12].

Oxaliplatin, a third-generation platinum analogue, is a diamminocyclohexane platinum which forms interstrand DNA adducts, which differ from those formed by cisplatin or carboplatin in terms of their capability to overcome resistance mechanisms. Preclinical studies have suggested that pancreatic cancer cell lines are highly sensitive towards raltitrexed and oxaliplatin even in gemcitabine- and 5-fluorouracil-resistant cells [13, 14], and oxaliplatin evidences an additive antitumor activity when combined with raltitrexed or other thymidylate synthase inhibitors [15].

Herein, we have attempted to confirm the efficacy and safety of a combination of irinotecan and oxaliplatin (IROX) as a salvage treatment for patients with gemcitabine- and 5-FU-refractory pancreatic cancer.

Patients and methods

Eligibility

The patients had to have a histologically confirmed diagnosis of adenocarcinoma of the pancreas, as well as at least one measurable lesion. Our study population included patients who had received a previous palliative gemcitabine-based and/or 5-FU based chemotherapy regimen. Cases evidencing progression within 6 months after adjuvant chemotherapy as gemcitabine and/or 5-FU were eligible for inclusion in the study. The Eastern Cooperative Oncology Group (ECOG) performance status was 0–2 in all patients in this study. The patients were also required to harbor no central nervous system metastases, no active infections, no serious or uncontrolled concurrent medical illnesses, and no previous history of any other malignancies. Adequate bone marrow function (absolute neutrophil count (ANC) $\geq 1500 \times 10^3 / \mu\text{L}$, platelet count $\geq 75,000 \times 10^3 / \mu\text{L}$), renal function (serum creatinine $\leq 1.5 \text{ mg/dL}$), and hepatic function (aspartate aminotransferase, alanine aminotransferase $\leq 3 \times$ upper limits of normal, total bilirubin $\leq 1.5 \times$ upper limits of normal) were essential. The study was approved by the local ethics committee, and informed consent was obtained from all patients prior to their entry in this study.

Treatment protocol and evaluation

Patients received oxaliplatin 85 mg/m^2 diluted in 500 ml of 5% dextrose as a 2-hr intravenous infusion on day 1, followed by 150 mg/m^2 of irinotecan diluted in 500 ml 5% dextrose as a 90-min infusion once every 2 weeks. Treatment was continued until signs of disease progression or unacceptable toxic effects developed, or until a patient refused further treatment.

Dose modification for toxicity

Administration of irinotecan or oxaliplatin was delayed if there were non-hematologic toxicities of the National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 3 or greater, neutropenia of less than $1,500 / \mu\text{L}$, or thrombocytopenia of less than $100,000 / \mu\text{L}$. If the neutrophil count was greater than $1,500 / \mu\text{L}$ and the

Table 1 Patients characteristics

No.	Sex	Age	ECOG PS	Previous OP	Adjuvant treatment ^a	Definitive CCRT ^a	Previous chemotherapy	Metastasis	Cycles	Response	TTP (months)	OS (months)
1	M	48	2	No		RT+X	Gem/Cis	Liver, distant LN	2	PD	0.7	2.2
2	M	73	1	No			Gem/S-1	Liver, lung, bone	2	PD	1.4	3.0
3	M	69	1	No			Gem/S-1	Liver	6	PR	7.4	14.4
4	F	57	2	No			Gem/Cis -> X	Peritoneal seeding	3	SD	7.5	7.7
5	M	67	1	Yes	RT+X		Gem	Liver	2	SD	5.2	5.2
6	M	73	1	No			Gem/S-1 -> Gem/Cis	Liver, distant LN	12	PR	6.2	6.9 ^b
7	F	58	1	Yes	FL		Gem	Liver, peritoneal seeding	3	SD	4.2	5.1
8	M	62	2	No			Gem/5-FU	Liver	1	PD	0.6	1.5
9	M	53	2	No			Gem/Cis -> FAM	Liver, lung, omentum, diaphragm	1	PD	0.9	1.1
10	M	64	1	No			GemX	Liver, distant LN, bone	2	SD	1.3	2.6 ^b
11	M	70	1	Yes	RT+X		Gem	Distant LN	2	PD	0.8	3.1
12	M	67	1	Yes ^c			Gem/5-FU	Liver	2	PD	0.9	4.1
13	M	67	1	No			Gem/S-1->Gem/Cis	Liver	3	PD	1.4	3.9
14	F	48	1	No			Gem/S-1	SMA,SMV	9	PR	4.6	10.5

^a Progression within 6 months after treatment, ^b Alive status, ^c Palliative operation

ECOG PS Eastern Cooperative Oncology Group Performance status, M male, F female, OP operation, CCRT concurrent chemo-radiotherapy, RT radiotherapy, TTP time to progression, OS overall survival, PR partial response, SD stable disease, PD progressive disease, X capecitabine, FL 5-fluorouracil (5-FU)+leucovorin, Gem gemcitabine, S-1; TS-1, Cis cisplatin, FAM 5-FU+adriamycin+mitomycin-C, LN lymph node, SMA superior mesenteric artery, SMV superior mesenteric vein

platelet count was greater than 100,000 / μ L after a one-week delay, chemotherapy was administered without dose reduction. If the ANC was less than 1,500 / μ L or the platelet count was less than 100,000 / μ L after a one-week delay, chemotherapy was delayed for an additional week. In cases in which patients required a delay of longer than 2 weeks for recovery, the patients were taken out of the study. The dose of irinotecan or oxaliplatin was reduced by 25% of the previous dose in cases of toxicities of NCI-CTC grade 3 or greater, diarrhea or mucositis, febrile neutropenia, or hemorrhagic complications due to thrombocytopenia.

Assessment of response

Physical examination, complete blood counts, chemistry, and chest x-rays were conducted after each cycle. Computed tomography (CT) scans were repeated every two cycles, or earlier in cases of clinical deterioration. The responses were evaluated in accordance with RECIST criteria [16]. Complete response (CR) was defined as the disappearance of all evidence of disease and the normalization of tumor markers persisting for at least 2 weeks. Partial response (PR) was defined as $\geq 30\%$ reduction in uni-dimensional tumor measurements, without the appearance of any new lesions or progression in any existing lesion. Progressive disease (PD) was defined as any of the following: (I) a 20% increase in the sum of the products of all measurable lesions, (II) the appearance of any new lesion, or (III) the reappearance of any lesion that had previously disappeared. Stable disease (SD) was defined as a tumor response that did not fulfill the criteria for CR, PR, or PD.

Dose intensity ($\text{mg}/\text{m}^2/\text{week}$) was calculated as the total cumulative dose divided by the duration of treatment. Relative dose-intensity (RDI) was calculated by dividing the dose-intensity by the planned dose-intensity, and was expressed as a percentage. Planned dose-intensities, which were expressed in terms of $\text{mg}/\text{m}^2/\text{week}$, were 75 for irinotecan and 42.5 for oxaliplatin.

Statistical methods

Time to progression (TTP) and overall survival (OS) rates were calculated via the Kaplan-Meier method. The response duration was defined as the period of time from the initial date of response to treatment to the time of disease progression or recurrence. The time to progression and overall survival were calculated from the initiation of treatment to the first observation of disease progression or death, respectively. All data were analyzed with SPSS software (version 15.0, Chicago-IL)

Results

Patient characteristics

Between May 2006 and December 2008, a total of 14 patients were assigned for treatment at the Gyeongnam Regional Cancer Center, in Jinju, South Korea. The basal characteristics of the patients are listed in Table 1. The male-to-female ratio was 11:3. The median patient age was 65.5 years (range: 48–73 years), and 71.4% (10/14) of the patients exhibited an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

The most frequent metastatic site or site of involvement was the liver (78.6%), followed by the distant lymph node (28.6%), and the peritoneum (21.4%), in order of decreasing frequency. All 14 of the patients had been treated with gemcitabine and 5-FU (intravenous or oral) as a palliative chemotherapy. Response to first-line chemotherapy was PR in seven patients (50%) and SD in two patients (14.3%).

Response and survival

The median follow-up duration was 12.7 months (range: 7.0–32.2 months). Among the 14 patients evaluated for their tumor responses, three achieved a partial response, with an overall response rate of 21.4% (95% confidence interval [CI]: 0.0–46.0%). Four patients (28.6%) evidenced stable disease and seven patients (50%) evidenced progression during the course of treatment (Table 2). The median time to progression was 1.4 months (95% CI: 1.2–1.6 months), and the median overall survival time was 4.1 months (95% CI: 2.0–6.2 months) (Fig. 1).

Dose administration and toxicity

14 patients received a total of 50 treatment cycles. Dose reduction was conducted over 23 cycles (46%). The dose intensity ($\text{mg}/\text{m}^2/\text{wk}$) was 62.9 (83.9%) for irinotecan and 36.2 (85.1%) for oxaliplatin. The median number of cycles of IROX treatment was 2 (range, 1–12 cycles). The toxicities observed during the treatment are provided in

Table 2 Response of treatment

Response	N=14	%
CR	0	0
PR	3	21.4
SD	4	28.6
PD	7	50

CR complete response, PR partial response, SD stable disease, PD progression of disease

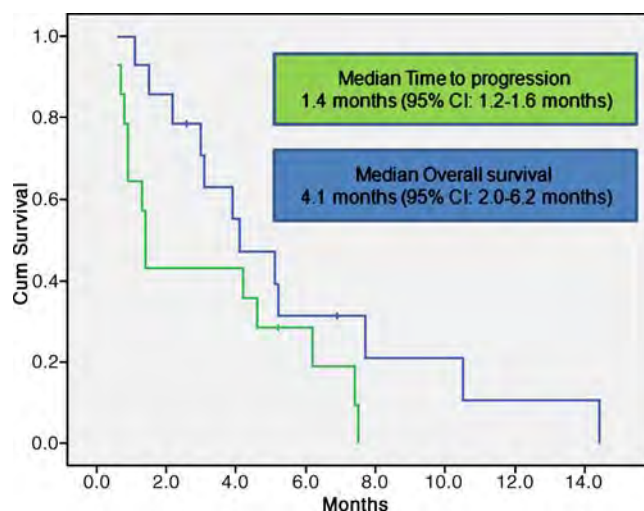


Fig. 1 Time to progression and overall survival curves

Table 3. Grade 1 or 2 anemia and neutropenia were observed in 44 cycles (88%) and 18 cycles (36%), respectively. Grade 3 or 4 neutropenia was observed in 5 cycles (10%), and febrile neutropenia occurred in two cycles (4%). Grade 3 nausea and diarrhea were observed in 1 and 2 patients, respectively. Grade 1 AST/ALT increase was observed in one patient, and grade 1 neuropathy was also observed in 1 patient.

Discussion

Gemcitabine has been commonly employed as the standard chemotherapeutic agent for the treatment of advanced

Table 3 Toxicity of treatment

	NCI-CTC ^b grade (%)			
	1	2	3	4
Hematologic^a (N=50)				
Anemia	31 (62)	13 (26)		
Neutropenia	13 (26)	5 (10)	2 (4)	3 (6)
Thrombocytopenia	13 (26)	2 (4)		
Non-hematologic^b (N=14)				
Nausea			1 (7)	
Diarrhea			2 (14)	
AST/ALT	2 (14)			
Neuropathy	1 (7)			

^a Per cycle

^b Per person, maximum toxicity of each patient

NCI-CTC National Cancer Institute-Common Toxicity Criteria v3.0, AST Aspartic acid transaminase, ALT Alanine aminotransferase

Table 4 Clinical trials in the salvage treatment of pancreatic cancer

Study	Regimen	Status of treatment	No.	RR (%)	TTP (months)	OS (months)
Cantore [22]	Irinotecan/oxaliplatin	Pretreated	30	10	4.1	5.9
Ulrich-Pur [23]	Raltitrexed/irinotecan	Gemcitabine-refractory	19	16	4.0	6.5
Reni [24]	Raltitrexed/oxaliplatin	Gemcitabine-refractory	41	24	NA	5.2
Ignatiadis [25]	Docetaxel/egfinitib	Gemcitabine-refractory	26	19	2.1	2.9
Tsavaris [21]	Oxaliplatin/LV/5-FU	Gemcitabine-refractory	30	23	5.2	6.2
Yi [26]	Irinotecan	Gemcitabine-refractory	33	9	2.0	6.6
Burris [27]	Rubitecan	Pretreated	43	7	2.0	3.0
Oettle [28]	Oxaliplatin/LV/5-FU	Gemcitabine-refractory	23	NR	NR	5.2
Oh [this study]	Irinotecan/oxaliplatin	Gemcitabine and 5-FU refractory	14	21	1.4	4.1

RR response rate, TTP time to progression, OS overall survival, LV leucovorin, 5-FU 5-fluorouracil, NR not reported

pancreatic cancer [1]. 5-FU is also extensively utilized as an adjuvant chemotherapy, a chemoradiotherapeutic agent for patients with locally advanced pancreatic cancer, and a gemcitabine-combined or gemcitabine-refractory salvage chemotherapy in cases of metastatic pancreatic cancer [17–21]. However, the low response rate and early disease progression are requirements for the salvage treatment of pancreatic cancer. Several candidate agents—irinotecan, oxaliplatin, docetaxel, gefitinib, raltitrexed, and rubitecan—have been assessed for their possible efficacy as a second-line therapy for patients who refractory to gemcitabine (Table 4) [21–27]. There is, however, no consensus regarding second-line therapy for patients with gemcitabine refractory disease. Furthermore, it is questionable that salvage chemotherapy for patients with advanced pancreatic cancer will result in prolonged survival, and there remains some potential for toxicity from the treatment. In a randomized phase III trial after the failure of first-line gemcitabine, BSC plus with biweekly oxaliplatin combined with weekly 5-FU as a 24-hour infusion plus leucovorin (OFF) was compared to BSC alone. After 46 patients out of 165 planned, the BSC arm had to be closed because BSC alone was no longer accepted by participating center, with a possible survival benefit for second-line chemotherapy (21 weeks in OFF group versus 10 weeks in BSC group) [28]. After this, preliminary data from a clinical trial in which OFF was randomly compared with 5-FU/leucovorin provided the first evidence for a possible survival benefit associated with the use of oxaliplatin in a second-line setting. Irinotecan monotherapy or combination with other drugs has also been shown to be marginally effective and well tolerated in gemcitabine refractory second-line treatment.

Combined irinotecan and oxaliplatin treatment in patients pre-treated with advanced pancreatic cancer evidenced a response rate of 10% and overall survival duration of 5.9 months [22].

In our study, the overall response and disease control rates were 21.4% and 50%, respectively. Even though all patients were refractory to gemcitabine and 5-FU, this response rate was comparable to previous second-line trials— which were concerned principally with gemcitabine refractoriness. However, time to progression and overall survival duration (1.4 months and 4.1 months) were slightly shorter than has been reported in other studies. This may be because eight out of 14 patients (57%) were treated with IROX as a third-line treatment, and 28.6% of patients had poor performance status (ECOG 2). Performance status of patients has been a crucial role to determine whether to receive salvage treatment or not. In our data, patients with performance status of ECOG 1 had tendency to have longer survival duration than ECOG 2 (5.1 month versus 1.5 months, $P=0.077$).

The dosages of the irinotecan and oxaliplatin administered in our study were somewhat higher than in IROX

regimens that had been utilized in the treatment of colorectal cancer (oxaliplatin 85 mg/m² and irinotecan 200 mg/m² on day 1 administered every 3 weeks) and non-small cell lung cancer (oxaliplatin 130 mg/m² day 1 and irinotecan 65 mg/m² on day 1 and day 8 every 3 weeks) [29, 30]. However, hematologic and non-hematologic toxicities were not increased as compared with those reports, and these effects are manageable with symptomatic supportive care.

The results of this exploratory study demonstrate that the IROX regimen appears to constitute a feasible and tolerable salvage therapy in patients with advanced pancreatic cancer who had been previously treated with gemcitabine- and 5-FU-based chemotherapy. Further exploration into IROX combination treatment for patients with gemcitabine- and 5-FU- refractory pancreatic cancer is clearly warranted.

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References

- Burris HA III, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD (1997) Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 15:2403–2413
- Herrmann R, Bodoky G, Ruhstaller T, Glimelius B, Bajetta E, Schuller J, Saletti P, Bauer J, Figier A, Pestalozzi B, Kohne CH, Mingrone W, Stemmer SM, Tamas K, Kornek GV, Koeberle D, Cina S, Bernhard J, Dietrich D, Scheithauer W (2007) Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. *J Clin Oncol* 25:2212–2217. doi:10.1200/JCO.2006.09.0886
- Moore MJ, Goldstein D, Hamm J, Figier A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, Campos D, Lim R, Ding K, Clark G, Voskoglou-Nomikos T, Ptasynski M, Parulekar W (2007) Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 25:1960–1966. doi:10.1200/JCO.2006.07.9525
- Ducreux M, Boige V, Malka D (2007) Treatment of advanced pancreatic cancer. *Semin Oncol* 34:S25–S30. doi:10.1053/j.seminoncol.2007.01.006
- Heinemann V, Boeck S, Hinke A, Labianca R, Louvet C (2008) Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. *BMC Cancer* 8:82. doi:10.1186/1471-2407-8-82
- Evans DB, Lee JE, Pisters PW, Charnsangavej C, Ellis LM, Chiao PJ, Lenzi R, Abbruzzese JL (1997) Advances in the diagnosis and treatment of adenocarcinoma of the pancreas. *Cancer Treat Res* 90:109–125
- Glimelius B, Hoffman K, Sjoden PO, Jacobsson G, Sellstrom H, Enander LK, Linne T, Svensson C (1996) Chemotherapy

- improves survival and quality of life in advanced pancreatic and biliary cancer. *Ann Oncol* 7:593–600
8. Creemers GJ, Lund B, Verweij J (1994) Topoisomerase I inhibitors: topotecan and irinotecan. *Cancer Treat Rev* 20:73–96. doi:10.1016/0305-7372(94)90011-6
 9. Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, Jandik P, Iveson T, Carmichael J, Alakl M, Gruia G, Awad L, Rougier P (2000) Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 355:1041–1047. doi:10.1016/S0140-6736(00)02034-1
 10. Saltz LB, Cox JV, Blanke C, Rosen LS, Fehrenbacher L, Moore MJ, Maroun JA, Ackland SP, Locker PK, Pirotta N, Elfiring GL, Miller LL (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 343:905–914. doi:10.1056/NEJM200009283431302
 11. Bissery MC, Vrignaud P, Lavelle F, Chabot GG (1996) Experimental antitumor activity and pharmacokinetics of the camptothecin analog irinotecan (CPT-11) in mice. *Anticancer Drugs* 7:437–460. doi:10.1097/00001813-199606000-00010
 12. Wagener DJ, Verdonk HE, Dirix LY, Catimel G, Siegenthaler P, Buitenhuis M, Mathieu-Boue A, Verweij J (1995) Phase II trial of CPT-11 in patients with advanced pancreatic cancer, an EORTC early clinical trials group study. *Ann Oncol* 6:129–132
 13. Kornmann M, Fakler H, Butzer U, Beger HG, Link KH (2000) Oxaliplatin exerts potent in vitro cytotoxicity in colorectal and pancreatic cancer cell lines and liver metastases. *Anticancer Res* 20:3259–3264
 14. Monti P, Marchesi F, Reni M, Mercalli A, Sordi V, Zerbi A, Balzano G, Di Carlo V, Allavena P, Piemonti L (2004) A comprehensive in vitro characterization of pancreatic ductal carcinoma cell line biological behavior and its correlation with the structural and genetic profile. *Virchows Arch* 445:236–247. doi:10.1007/s00428-004-1053-x
 15. Raymond E, Faivre S, Woynarowski JM, Chaney SG (1998) Oxaliplatin: mechanism of action and antineoplastic activity. *Semin Oncol* 25:4–12
 16. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States. *National Cancer Institute of Canada. J Natl Cancer Inst* 92:205–216. doi:10.1093/jnci/92.3.205
 17. Neoptolemos JP, Stocken DD, Tudur Smith C, Bassi C, Ghaneh P, Owen E, Moore M, Padbury R, Doi R, Smith D, Buchler MW (2009) Adjuvant 5-fluorouracil and folinic acid vs observation for pancreatic cancer: composite data from the ESPAC-1 and -3(v1) trials. *Br J Cancer* 100:246–250. doi:10.1038/sj.bjc.6604838
 18. Kim HM, Bang S, Park JY, Seong J, Song SY, Chung JB, Park SW (2009) Phase II trial of S-1 and concurrent radiotherapy in patients with locally advanced pancreatic cancer. *Cancer Chemother Pharmacol* 63:535–541. doi:10.1007/s00280-008-0836-1
 19. Lee S, Oh SY, Kim BG, Kwon HC, Kim SH, Rho MH, Kim YH, Rho MS, Jeong JS, Kim HJ (2009) Second-Line Treatment With a Combination of Continuous 5-Fluorouracil, Doxorubicin, and Mitomycin-C (Conti-Fam) in Gemcitabine-Pretreated Pancreatic and Biliary Tract Cancer. *Am J Clin Oncol* [Epub ahead of print]
 20. Kim YJ, Bang S, Park JY, Park SW, Chung JB, Song SY (2009) Phase II study of 5-fluorouracil and paclitaxel in patients with gemcitabine-refractory pancreatic cancer. *Cancer Chemother Pharmacol* 63:529–533. doi:10.1007/s00280-008-0822-7
 21. Tsavaris N, Kosmas C, Skopelitis H, Gouveris P, Kopterides P, Loukeris D, Sigala F, Zorbala-Sypsa A, Felekouras E, Papalambros E (2005) Second-line treatment with oxaliplatin, leucovorin and 5-fluorouracil in gemcitabine-pretreated advanced pancreatic cancer: A phase II study. *Invest New Drugs* 23:369–375. doi:10.1007/s10637-005-1446-y
 22. Cantore M, Rabbi C, Fiorentini G, Oliani C, Zamagni D, Iacono C, Mambrini A, Del Freato A, Manni A (2004) Combined irinotecan and oxaliplatin in patients with advanced pre-treated pancreatic cancer. *Oncology* 67:93–97. doi:10.1159/000080993
 23. Ulrich-Pur H, Raderer M, Verena Kornek G, Schull B, Schmid K, Haider K, Kwasny W, Depisch D, Schneeweiss B, Lang F, Scheithauer W (2003) Irinotecan plus raltitrexed vs raltitrexed alone in patients with gemcitabine-pretreated advanced pancreatic adenocarcinoma. *Br J Cancer* 88:1180–1184. doi:10.1038/sj.bjc.6600883
 24. Reni M, Pasetto L, Aprile G, Cordio S, Bonetto E, Dell’Oro S, Passoni P, Piemonti L, Fugazza C, Luppi G, Milandri C, Nicoletti R, Zerbi A, Balzano G, Di Carlo V, Brandes AA (2006) Raltitrexed-eloxatin salvage chemotherapy in gemcitabine-resistant metastatic pancreatic cancer. *Br J Cancer* 94:785–791. doi:10.1038/sj.bjc.6603026
 25. Ignatiadis M, Polyzos A, Stathopoulos GP, Tselepatiotis E, Christophylakis C, Kalbakis K, Vamvakas L, Kotsakis A, Potamianou A, Georgoulas V (2006) A multicenter phase II study of docetaxel in combination with gefitinib in gemcitabine-pretreated patients with advanced/metastatic pancreatic cancer. *Oncology* 71:159–163. doi:10.1159/000106064
 26. Yi SY, Park YS, Kim HS, Jun HJ, Kim KH, Chang MH, Park MJ, Uhm JE, Lee J, Park SH, Park JO, Lee JK, Lee KT, Lim HY, Kang WK (2009) Irinotecan monotherapy as second-line treatment in advanced pancreatic cancer. *Cancer Chemother Pharmacol* 63:1141–1145. doi:10.1007/s00280-008-0839-y
 27. Burris HA III, Rivkin S, Reynolds R, Harris J, Wax A, Gerstein H, Mettinger KL, Staddon A (2005) Phase II trial of oral rubitecan in previously treated pancreatic cancer patients. *Oncologist* 10:183–190. doi:10.1634/theoncologist.10-3-183
 28. Oettle H, Pelzer U, Stieler J, Hilbig A, Roll L, Schwaner I, Adler M, Detken S, Dörken B, Riess H (2005) Oxaliplatin/folic acid/5-fluorouracil [24 h] (OFF) plus best supportive care versus best supportive care alone (BSC) in second-line therapy of gemcitabine refractory advanced pancreatic cancer (CONKO 003). *J Clin Oncol* 23:201s, abstract 4031
 29. Ashley AC, Sargent DJ, Alberts SR, Grothey A, Campbell ME, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC, Goldberg RM (2007) Updated efficacy and toxicity analysis of irinotecan and oxaliplatin (IROX) : intergroup trial N9741 in first-line treatment of metastatic colorectal cancer. *Cancer* 110:670–677. doi:10.1002/cncr.22831
 30. Chang MH, Kim KH, Jun HJ, Kim HS, Yi SY, Uhm JE, Park MJ, Lim DH, Ji SH, Hwang IG, Lee J, Park YH, Ahn JS, Ahn MJ, Park K (2009) Irinotecan and oxaliplatin combination as the first-line treatment for patients with advanced non-small cell lung cancer. *Cancer Chemother Pharmacol* [Epub ahead of print]

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Appendix OZAKA02



A phase II study of modified FOLFIRINOX for chemotherapy-naïve patients with metastatic pancreatic cancer

Masato Ozaka¹ · Hiroshi Ishii² · Tosiya Sato³ · Makoto Ueno⁴ · Masafumi Ikeda⁵ · Kazuhiro Uesugi² · Naohiro Sata⁶ · Kouichirou Miyashita⁷ · Nobumasa Mizuno⁸ · Kunihiro Tsuji⁹ · Takuji Okusaka¹⁰ · Junji Furuse¹¹

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Abstract

Background We evaluated the efficacy and safety of a modified FOLFIRINOX regimen for chemotherapy-naïve patients with metastatic pancreatic cancer.

Methods Patients with untreated metastatic pancreatic cancer (MPC) received modified FOLFIRINOX (intravenous oxaliplatin 85 mg/m², irinotecan 150 mg/m², 5-FU infusion 2400 mg/m² over 46 h, no bolus 5-FU). The primary endpoints were overall survival and the incidence of grade 3 or higher neutropenia. No patients received prophylactic pegfilgrastim.

Results Sixty-nine pts. were enrolled from 39 institutions in Japan. The median overall survival was 11.2 months [95% confidence interval (CI) 9.0–]. The median progression-free survival was 5.5 months (95% CI 4.1–6.7). The response rate was 37.7% (95% CI 26.3–50.2), and the disease control rate was 78.3% (95% CI 66.7–87.3). The incidence of grade 3 or higher neutropenia was 47.8%. Serious adverse events occurred in six patients (8.7%). All AE proportions were less than those in the previous Japanese full-dose phase II study. One patient died due to interstitial pneumonia related to treatment.

Conclusion This is the first prospective study of modified FOLFIRINOX in Asia. Modified FOLFIRINOX in this study has an improved safety profile with maintained efficacy in MPC without prophylactic pegfilgrastim.

Keywords Metastatic · Pancreatic cancer · Chemotherapy · FOLFIRINOX · Modified FOLFIRINOX

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Introduction

Pancreatic cancer is a highly lethal cancer with a 2–3% 5-year survival rate and is the fourth leading cause of cancer-related mortality in Japan. In the phase III study (ACCORD11 trial) conducted by Conroy et al., FOLFIRINOX (FFX: oxaliplatin, irinotecan, 5-FU and leucovorin) showed a significant improvement in overall survival, progression-free survival and quality of life compared with gemcitabine [1]. From the results of the ACCORD11 trial, FFX is currently acknowledged as one of the standard therapies for chemotherapy-naïve patients with metastatic pancreatic cancer (MPC), with good performance status. However, in the ACCORD11 trial, the incidence rates of neutropenia and febrile neutropenia in the FFX arm were reported as 45.3 and 5.4%, respectively. This was significantly higher than in the gemcitabine arm. Furthermore, it was found to be more toxic when used in real clinical situations than previously indicated by the ACCORD11 trial, so regimens with a reduced dosage have been used at many hospitals [2]. Many of the recent FFX-related clinical trials were conducted using a modified regimen by omitting the 5FU bolus.

In Japan, a phase II trial of FFX was conducted for 36 patients with metastatic pancreatic cancer [3]. The efficacy in the Japanese phase II study was similar to that reported in the ACCORD11 trial, and the incidences of grade 3 or 4 toxicities, especially neutropenia (77.8%) and febrile neutropenia (22.2%), were higher. Although the standard FFX has a greater effectiveness based on the data of the Japanese/ACCORD11 trial, it is considered that the management of adverse events could still be difficult. The trial was planned because we considered it necessary upfront to perform dose reductions for the 5FU bolus and irinotecan in patients with MPC to develop a safer FFX therapy while maintaining its efficacy. We report the analysis of the efficacy and toxicity of modified FFX in MPC.

Materials and methods

Patients

The inclusion criteria were as follows: histologically or cytologically confirmed pancreatic adenocarcinoma or adenosquamous carcinoma; an Eastern Cooperative Oncology Group PS of 0 or 1; age 20–75 years; MPC with at least one measurable lesion; and adequate haematological, liver, and renal function (haemoglobin ≥ 9.0 g/dL, white blood cell count $\leq 10,000/\text{mm}^3$, neutrophil count $\geq 2000/\text{mm}^3$, platelet count $\geq 100,000/\text{mm}^3$, total bilirubin $\leq$ upper limit

of normal, aspartate transaminase and alanine transaminase ≤ 2.5 upper limit of normal, creatinine ≤ 1.2 mg/dL, and C-reactive protein ≤ 2.0 mg/dL). Patients were excluded if they had the following: prior chemotherapy or radiation therapy; grade 2 or higher peripheral sensory neuropathy; blood transfusion, blood products, or haematopoietic growth factor preparations such as G-CSF within 7 days before enrolment; UGT genetic polymorphisms of homozygous UGT1A1*28 or UGT1A1*6 or heterozygous UGT1A1*6 and UGT1A1*28; apparent coelomic fluid (pleural effusion, ascites, or pericardial fluid) or peritoneal cancer dissemination; diarrhoea including watery stools within 3 days before enrolment; poorly controlled diabetes; synchronous or metachronous double cancer, excluding carcinoma in situ or intramucosal carcinoma cured by local treatment; active infection; or other serious concomitant diseases.

Study design

This study was an open-label, multicentre, single-arm phase II study.

The primary endpoints were overall survival (OS) and the incidence of grade 3 or higher neutropenia, and the secondary endpoints were progression-free survival (PFS), response rate and safety for all of the patients. This clinical trial was conducted with the approval of the review board of each participating institution and in accordance with the Declaration of Helsinki. This trial is registered with UMIN-CTR (<http://www.umin.ac.jp/ctr/index-j.htm>), identification number (UMIN000013301).

Treatment

Patients were treated with modified FFX every 2 weeks, as follows: 2-h i.v. infusion of oxaliplatin at 85 mg/m^2 and 2-h i.v. infusion of l-leucovorin at 200 mg/m^2 . Irinotecan was also i.v. infused over 90 min at 150 mg/m^2 , followed by continuous i.v. infusion of 5-FU over 46 h at 2400 mg/m^2 . Bolus 5-FU was omitted. All patients routinely received palonosetron, aprepitant and dexamethasone for emesis prophylaxis. G-CSF was not allowed as primary prophylaxis. The treatment was continued until disease progression, unacceptable toxicity, discontinuation as decided by the investigators, or patient refusal.

Chemotherapy was delayed until recovery from the following criteria: neutrophil count $< 1500/\text{mm}^3$, platelet count $< 75,000/\text{mm}^3$, total bilirubin > 1.5 mg/dL, grade 3 or higher peripheral sensory neuropathy, grade 2 or higher diarrhoea, and watery stools.

When the predefined toxic events in the protocol occurred, dose adjustment was required. The reduced dose was set at 120 and 100 mg/m^2 for irinotecan, 65 and 50 mg/

m² for oxaliplatin, and 1800 and 1200 mg/m² for infusional 5-FU.

Assessment

Patients were evaluated for toxicities at the start of each cycle. Complete blood counts, blood chemical tests, and physical examinations were carried out every 2 weeks. Computed tomography was carried out at least every 6 weeks. Tumour response was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. OS was measured from the date of enrolment to the date of death or the date of the last follow-up. PFS was defined as the time from the date of enrolment to the first documentation of disease progression or death. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Statistical analysis

The expected and threshold OS times for the modified FFX regimen were set as 11 and 7 months, respectively, on the basis of the OS associated with gemcitabine and FFX (6.8 and 11.1 months, respectively) in the ACCORD11 trial. Assuming an exponential distribution for OS, we calculated 60 participants required to provide the trial with 80% power to detect a 36% improvement in median OS at a one-sided significance level of 2.5%. Accordingly, the target sample size was set at 65 subjects to account for the exclusion of patients. The median survival time and corresponding 95% CIs for OS and PFS were estimated using the Kaplan–Meier method.

Results

Patient characteristics

Between February 2014 and December 2014, 69 patients were enrolled (Fig. 1). The patient characteristics at baseline are shown in Table 1. The median age was 62.6 years (range 42–74), 68.1% of the patients had a PS 0, the primary site of the tumour was the head of the pancreas in 44.9% of patients, 20.3% of patients had a biliary stent, and 2.8% of patients experienced recurrence after resection. The major sites of metastasis were the liver and lymph nodes. All 69 patients received the study drugs and met the eligibility criteria.

Treatment

The median number of treatment cycles was eight (range 1–25). The median relative dose intensities of oxaliplatin,

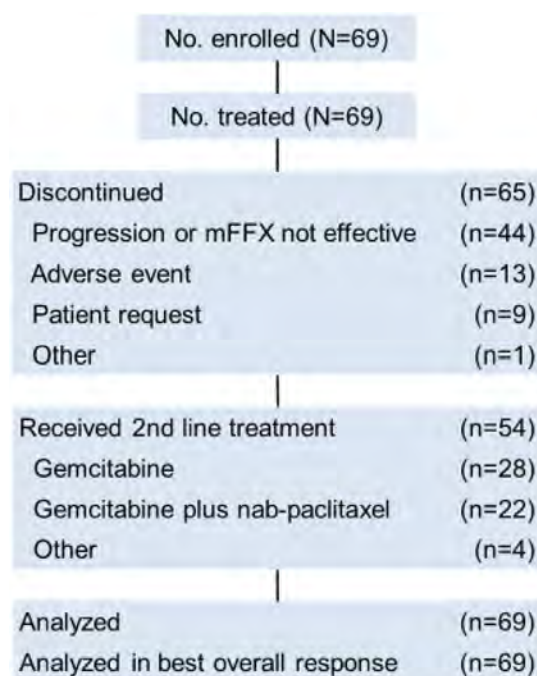


Fig. 1 Patient disposition

irinotecan, infusional 5-FU, and l-leucovorin were 76.1, 91.4, 95.4 and 99.1%, respectively. Dose reduction and treatment delay occurred in 54 patients (79.7%). Neutropenia was the most frequent cause of both dose reduction and treatment delay. The major reasons for discontinuation of the treatment were disease progression (67.7%) and adverse event (20%). Of the 69 enrolled patients, 54 received second-line treatment. The most common treatment comprised gemcitabine, which was given to 28 patients. The other regimen was gemcitabine + nab-paclitaxel, which was given to 22 patients. There was no significant difference between the gemcitabine group and the gemcitabine + nab-paclitaxel group in PFS from the secondary treatment.

Efficacy

The objective RR and disease control rate in all patients were 37.7% (95% CI 26.3–50.2) and 78.3% (95% CI 66.7–87.3), respectively (Table 2). They were not significantly different from the response rate in patients in the FFX-treated historical control group.

Partial response, stable disease, and progressive disease were observed in 26, 28, and 10 patients, respectively. The median time to partial response was 76 days (range 35–252 days), and the median duration of response was 167 days (range 152–196 days).

Table 3 and Fig. 2 show the results for OS and PFS, respectively. The median OS was 11.2 months (95% CI 9.0–), and the 1-year survival rate was 48.1% (95% CI 36.1–60.1).

Table 1 Baseline characteristics of treated patients

Characteristics	N = 69	
	No. of patients	%
Age (years)		
Median	62.6	
Range	42.4–74.2	
Sex		
Female	26	37.7
Male	43	62.3
ECOG PS		
0	47	68.1
1	22	31.9
Pancreatic tumor cell type		
Adenocarcinoma	68	98.6
Squamous cell carcinoma	1	0.1
Pancreatic tumor location		
Head	31	44.9
Body	22	31.9
Tail	16	23.2
Measurable metastatic sites		
Liver	49	71.0
Lymph node	11	15.9
Lung	5	7.2
Other	3	4.3
Prior surgery		
Yes	4	5.8
No	65	94.2
Biliary stent		
Yes	14	20.3
No	55	79.7
CA19-9		
Median	1183.3	
Range	0.6–127,436	
1000 U/mg and less	33	47.8
Over 1000 U/mg	36	52.2

The median PFS was 5.5 months (95% CI 4.1–6.7) and the 1-year PFS rate was 21% (95% CI 11.2–30.7).

Adverse events

Grade 3 or 4 toxicities occurred in 49 patients (71%). The major grade 3 and 4 toxicities are summarized in Table 4. The major grade 3 or 4 haematological toxicities were neutropenia (47.8%), leucopenia (29%), and anaemia (4.3%). The incidence of febrile neutropenia was 8.7%. The incidences of grade 3 or 4 neutropenia (47.8 vs 77.8%) and febrile neutropenia (8.7 vs 22.2%) were significantly decreased in our study compared with the historical Japanese trial treated with standard FFX. Patients with severe neutropenia and febrile neutropenia were treated with G-CSF

Table 2 Summary of best response by RECIST criteria

Best response	n = 69	
	No. of patients	%
CR	0	
PR	26	37.7
SD	28	40.6
PD	10	14.5
Not evaluable	5	7.2
ORR (CR + PR)	26	37.7
Exact 95% CI		26.3–50.2
DCR (CR + PR + SD)	54	78.3
Exact 95% CI		66.7–87.3

CI confidence interval, CR complete response, DCR disease control rate, ORR overall response rate, PD progressive disease, PR partial response, SD stable disease

Table 3 Results of overall survival (OS) and progression-free survival (PFS)

	N = 69
OS	
No of events	38
Person-months	729.7
Median OS (months)	11.2
95% CI	9.0– ^a
1 year survival proportion	0.481
95% CI	0.361–0.601
Estimated hazard ^b	0.62
Exact 95% CI ^b	0.44–0.86
PFS	
No of events	59
Person-months	450.8
Median PFS (months)	5.5
95% CI	4.1–6.7
1 year PFS proportion	0.210
95% CI	0.112–0.307
Estimated hazard ^b	1.57
Exact 95% CI ^b	1.20–2.03

^a Upper limit was not calculated

^b per 12 person-months (1 person-year)

to control these toxicities, but only 18% of patients were treated with G-CSF. The major grade 3 and 4 non-haematological toxicities were as follows: anorexia (15.9%), diarrhoea (10.1%), fatigue (4.3%), nausea (8.7%), cholangitis (8.7%), thromboembolism (4.1%), and peripheral neuropathy (5.8%). Serious adverse events occurred in six patients (two duodenal perforation, two venous thromboembolisms, tumour haemorrhage and pneumonitis). There was one treatment-related death due to pneumonitis.

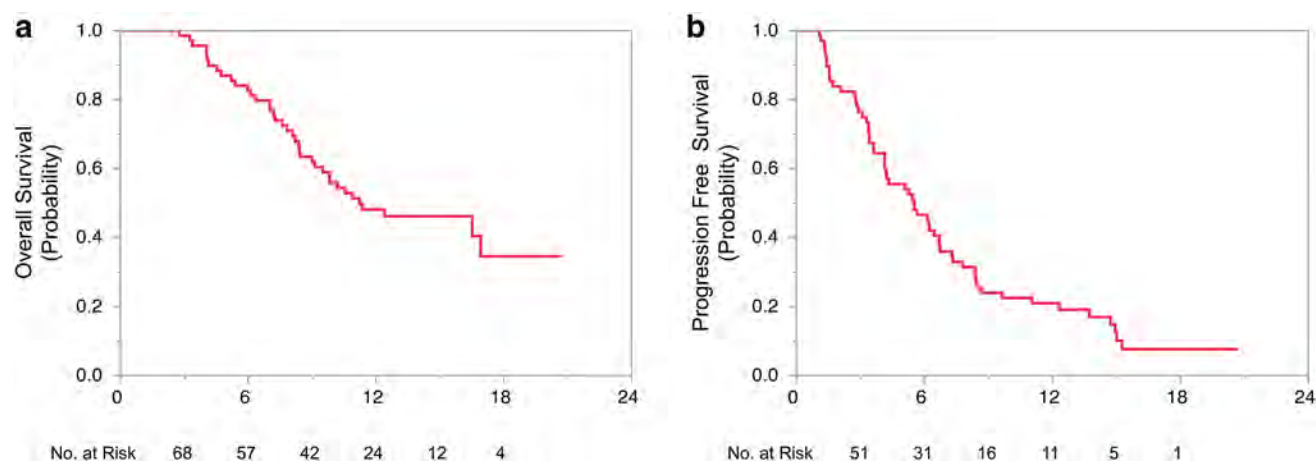


Fig. 2 **a** is Kaplan–Meier analysis of overall survival and **b** is progression-free survival

Table 4 Adverse events in chemotherapy-naïve Japanese patients with metastatic pancreatic cancer treated with modified FOLFIRINOX ($n = 69$)

	≥ Grade 3	
	<i>n</i>	%
Hematological toxicities		
Neutropenia	33	47.8
Leukopenia	20	29
Thrombocytopenia	2	2.9
Anemia	3	4.3
Non-hematological toxicities		
Febrile neutropenia	6	8.7
Anorexia	11	15.9
Diarrhoea	7	10.1
Nausea	6	8.7
Cholangitis	6	8.7
Fatigue	4	5.8
Peripheral sensory neuropathy	4	5.8
Infusion reaction	1	1.4

Discussion

This phase II trial was conducted to evaluate the efficacy and safety of reduced doses of FFX to mitigate adverse events.

In particular, in a Japanese phase II trial, febrile neutropenia was observed with a high frequency. To evaluate the efficacy and safety of modified FFX in this study, we needed to align the background with that of the Japanese phase II trial [3]. The demographics of the participants in the two trials were generally similar.

The features of the regimen in this study included the omission of the bolus 5FU and the reduced dose of

CPT-11 (to 150 mg). We omitted the bolus 5FU because of the results of the phase III trial to evaluate the efficacy of FOLFOXIRI (a regimen of FFX without a 5FU bolus, which was developed in Italy) for advanced colorectal cancer patients in comparison with FOLFIRI, which were presented by the Hellenic Oncology Research Group (HORG) in 2006 [4] and the Gruppo Oncologico Ovest (GONO) in 2007 [5], respectively. In the HORG trial, the median overall survival period in the FOLFOXIRI group was 21.5 months, and efficacy was not proven statistically when compared to the FOLFIRI group, whose survival period was 19.5 months ($p = 0.337$). However, the GONO trial showed significantly longer survival periods; the median overall survival period in the FOLFOXIRI group was 22.6 months, whereas it was 16.7 months in the FOLFIRI group. The reason that the GONO trial showed positive results was due to the omission of the 5FU bolus and the administered dose of the key drugs CPT-11 and L-OHP (L-OHP: 85 mg, CPT-11: 165 mg) (in the HORG regimen, L-OHP: 65 mg and CPT-11: 150 mg). In FFX for pancreatic cancer patients, CPT-11 and L-OHP were considered key drugs, and maintaining their dosages was very important. Furthermore, the median relative dose intensity of the 5FU bolus in the Japanese phase II trial was 15.9%. Thus, combined with the results of the phase III trial on colon cancer patients described above, we determined that the 5FU bolus had less significance in FFX therapy.

Moreover, the reason for reducing the dosage of CPT-11 was as follows: A phase I trial on FOLFOXIRI (GONO regimen) in the treatment of colon cancer patients was conducted in Japan [6]. For ten advanced colorectal cancer patients, the plan was to use the dose titration method and to increase the dosage level of L-OHP/CPT-11/5FU to 85/165/2400, 85/165/3200 and 85/185/3200 (mg/m²). However, dose-limiting toxicity (DLT) emerged due to a haematologic

toxicity of level 0, so the MTD was determined to be 85/165/2400 mg/m² and the RD was 85/150/2400 mg/m².

Furthermore, in a Japanese phase II trial on pancreatic cancer patients, the dosage of CPT-11 was reduced to 150 mg in 66.7% of patients after the second course, and only 10% of patients did not require reduction. We, therefore, believed that the reduction in CPT-11 in the modified FFX therapy was reasonable. Based on the Japanese phase I trial on colon cancer patients described above, we considered 150 mg to be appropriate for an initial dosage.

There is a risk that the efficacy could weaken due to the reduction in the initial dosage. However, the overall survival, which was the primary endpoint of this study, was almost the same as those in the ACCORD11 trial and the Japanese phase II trial. The other efficacy results were also similar to those of the previous standard FFX studies.

There are concerns that tumour shrinkage might be delayed by lowering the dosage at the start of therapy; however, tumour shrinkage was observed promptly after the start of therapy. Thus, there was no observable impact of reducing the dosage. We believe that the impact on the efficacy of the regimen when reducing the dose is minimal.

Furthermore, in this trial, we set the following provision: if a patient was determined to have sufficient tolerance in this modified regimen, they could return to their original regimen. In accordance with this provision, the dosage was increased for three patients; however, they showed obvious signs of haematologic toxicity with the increased dosage cycle, so we returned them to the reduced dosage regimen. This also indicates that the dosage used in this therapy has validity.

On the other hand, with respect to adverse events, a reduction in haematologic toxicity was observed due to the modified regimen. In particular, febrile neutropenia, which was frequently observed in the Japanese phase II trial, was suppressed and occurred at only a significantly low frequency. It should be noted that in this study, the rate of GCSF use during the study was only 18% among all patients, which was a low rate; however, the rate of occurrence of febrile neutropenia was suppressed.

The other modified FFX treatment showed favourable results in a previous report [7], but in that report, GCSF was used in all the cases. In this study, only 18% patients were treated with GCSF. Our modified FFX regimen is medico-economically very viable because the additional cost of GCSF is approximately \$1000.

When compared to the Japanese phase II trial, the results showed that satisfactory management of adverse events was possible while ensuring efficacy, but when compared to the ACCORD trial, the incidence of haematologic toxicity seemed to be higher. However, there were big differences between the ACCORD11 trial and the Japanese phase II trial in haematologic toxicity (the incidence of febrile

neutropenia: ACCORD; 5.4% and Japanese trial; 22.2%). In other carcinoma trials, it has been reported that the incidence of haematologic toxicity (especially febrile neutropenia) in non-Japanese trials is very different from that in the results of the Japanese trial. Most cases showed a higher febrile neutropenia incidence among Japanese patients breast cancer TC < DTX 75 + CPA 600 4 courses >: non-Japanese; 5%, Japanese; 68.8% [8, 9]; prostate cancer cabazitaxel 25 mg: non-Japanese; 8%, Japanese; 54.5% [10, 11], so there might be ethnic disparities in febrile neutropenia. Patients with the UGT1A1 mutation, which is deeply involved in the development of blood toxicity, were excluded both in the Japanese phase II trial and this trial. In these cases, the frequency of occurrence of blood toxicity was higher than in non-Japanese data. We assume that inter-ethnic differences might contribute to this difference, as non-Japanese subjects were included in other carcinoma cases, so adverse events should be compared between the Japanese data.

The limitations of this trial were that it was a single-arm phase II trial and we only had data on Japanese people. However, the efficacy of this modified regimen was similar to other global studies, and we found that the adverse events were well controlled compared to other Japanese groups, which have the same demographic balance of adverse events. Therefore, we believe this modified regimen to be one of the more effective FFX regimens.

One of the standard therapies for metastatic pancreatic cancer is gemcitabine + nab-paclitaxel (GnP). Compared to the original FFX, GnP is likely to be used because its adverse events are slightly mitigated [12]. However, if our modified FFX regimen is used, the same level of treatment can be expected with the same level of adverse events, so comparative trials between these two therapies are awaited in the future.

In conclusion, this is the first prospective study of modified FOLFIRINOX in Asia. The modified FOLFIRINOX regimen in this study has an improved safety profile with maintained efficacy in MPC without prophylactic pegfilgrastim.

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Compliance with ethical standards

Conflict of interest Masato Ozaka received the honoraria from Taiho Pharmaceutical, Yakult, Bayer, Pfizer and Novartis. Hiroshi Ishii is a member of a Data and safety Monitoring Board of Ono, and received the honoraria from Eisai, Taiho, Chugai and Astellas. Makoto Ueno

received honoraria from Abbott, Eli Lilly, Yakult and AstraZeneca and research funding from Eli Lilly, Kowa, Taiho, Yakult, Daiichi-Sankyo, Kyowa Hakko Kirin, Zeria, Merck Serono and AstraZeneca. Masafumi Ikeda received research funding from received research funding from GlaxoSmithKline, AstraZeneca, Yakult, Ono Pharmaceutical, and Eisai. Nobumasa Mizuno has received research grants from AstraZeneca, Eisai, Merck Serono, MSD, NanoCarrier, Taiho Pharmaceutical, and Zeria Pharmaceutical, and speakers bureau honoraria from Kyowa Hakko Kirin, Novartis, Pfizer, Taiho Pharmaceutical, and Yakult Honsha. Takuji Okusaka has had an editor role, research grant, and honoraria from Novartis; reports research grants and honoraria from Pfizer, Taiho, Bayer, Chugai, Eli Lilly and Company, Yakuruto Honsha, Ono Pharmaceutical, AstraZeneca, Merck Serono, Baxter, Nobelpharma Co.; and research grants from Nippon Boehringer Ingelheim, Daiippon Simitomo Pharma, Eisai Co., OncoTherapy Science Inc., Kyowa Hakko Kirin Co., Shizuoka Industry, Nano Carrier Co., Zeria Pharmaceutical Co. and Glaxo Smith Kline. Junji Furuse received has received honoraria from Taiho Pharmaceutical, Fujifilm, Eisai, Astellas, Yakult, Sumitomo Dainippon, Eli Lilly Japan, and Kyowa Hakko Kirin, and research funding from J-Pharma, Taiho Pharmaceutical, Ono Pharmaceutical, MSD, Janssen and Daiichi Sankyo. The other authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

References

- Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécauarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M (2011) FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 364:1817–1825
- Mahaseth H, Brucher E, Kauh J, Hawk N, Kim S, Chen Z, Kooby DA, Maithel SK, Landry J, El-Rayes BF (2013) Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. *Pancreas* 42:1311–1315
- Okusaka T, Ikeda M, Fukutomi A, Ioka T, Furuse J, Ohkawa S, Isayama H, Boku N (2014) Phase II study of FOLFIRINOX for chemotherapy-naïve Japanese patients with metastatic pancreatic cancer. *Cancer Sci* 105:1321–1326
- Souglakos J, Androulakis N, Syrigos K, Polyzos A, Ziras N, Athanasiadis A, Kakolyris S, Tsousis S, Kouroussis C, Vamvakas L, Kalykaki A, Samonis G, Mavroudis D, Georgoulis V (2006) FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG). *Br J Cancer* 94:798–805
- Falcone A, Ricci S, Brunetti I, Pfanner E, Allegrini G, Barbara C, Crinò L, Benedetti G, Evangelista W, Fanchini L, Cortesi E, Picone V, Vitello S, Chiara S, Granetto C, Porcile G, Fioretto L, Orlandini C, Andreuccetti M, Masi G (2007) Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the gruppo oncologico nord ovest. *J Clin Oncol* 25:1670–1676
- Sunakawa Y, Fujita K, Ichikawa W, Ishida H, Yamashita K, Araki K, Miwa K, Kawara K, Akiyama Y, Yamamoto W, Nagashima F, Saji S, Sasaki Y (2012) A phase I study of infusional 5-fluorouracil, leucovorin, oxaliplatin and irinotecan in Japanese patients with advanced colorectal cancer who harbor UGT1A1*1/*1,*1/*6 or *1/*28. *Oncology* 82:242–248
- Stein SM, James ES, Deng Y, Cong X, Kortmansky JS, Li J, Staugaard C, Indukala D, Boustani AM, Patel V, Cha CH, Salem RR, Chang B, Hochster HS, Lacy J (2016) Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer. *Br J Cancer* 114:737–743
- Jones SE, Savin MA, Holmes FA, O'Shaughnessy JA, Blum JL, Vukelja S, McIntyre KJ, Pippin JE, Bordelon JH, Kirby R, Sandbach J, Hyman WJ, Khandelwal P, Negron AG, Richards DA, Anthony SP, Mennel RG, Boehm KA, Meyer WG, Asmar L (2006) Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. *J Clin Oncol* 24:5381–5387
- Kosaka Y, Rai Y, Masuda N, Takano T, Saeki T, Nakamura S, Shimazaki R, Ito Y, Tokuda Y, Tamura K (2015) Phase III placebo-controlled, double-blind, randomized trial of pegfilgrastim to reduce the risk of febrile neutropenia in breast cancer patients receiving docetaxel/cyclophosphamide chemotherapy. *Support Care Cancer* 23:1137–1143
- de Bono JS, Oudard S, Ozguroglu M, Hansen S, Machiels JP, Kocak I, Gravis G, Bodrogi I, Mackenzie MJ, Shen L, Roessner M, Gupta S, Sartor AO (2010) Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 376:1147–1154
- Nozawa M, Mukai H, Takahashi S, Uemura H, Kosaka T, Onozawa Y, Miyazaki J, Suzuki K, Okihara K, Arai Y, Kamba T, Kato M, Nakai Y, Furuse H, Kume H, Ide H, Kitamura H, Yokomizo A, Kimura T, Tomita Y, Ohno K, Kakehi Y (2015) Japanese phase I study of cabazitaxel in metastatic castration-resistant prostate cancer. *Int J Clin Oncol* 20:1026–1034
- von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjuland SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF (2013) Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 369:1691–1703

Appendix PACHECO01



A systemic inflammation response index (SIRI) correlates with survival and predicts oncological outcome for mFOLFIRINOX therapy in metastatic pancreatic cancer

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ABSTRACT

Objectives: Systemic inflammatory response and survival has not been evaluated as a predictive factor of chemotherapy in metastatic pancreatic cancer. The aim of this study was to evaluate the prognostic and predictive value of a baseline Systemic Inflammation Response Index (SIRI) in metastatic pancreatic cancer.

Methods: Retrospective study of 164 metastatic pancreatic cancer patients. Associations between overall survival (OS), progression free survival (PFS), chemotherapy and SIRI were analyzed. SIRI is defined by neutrophil $\times$ monocyte/lymphocyte $10^9/L$.

Results: Median age 66 years. 22 (13%) received mFOLFIRINOX, 59 (36%) gemcitabine + nab-paclitaxel, 40 (24%) gemcitabine, 13 (8%) other regimens and 30 (18%) had not received treatment. Patients with $SIRI < 2.3 \times 10^9/L$ showed a statistically significant improvement in OS compared to $SIRI \geq 2.3 \times 10^9/L$ [16 months versus 4.8 months, Hazard Ratio (HR) 2.87, Confidence Interval (CI) 95% 2.02–4.07, $p < 0.0001$] that was confirmed in multivariate analysis. In addition, patients with $SIRI < 2.3 \times 10^9/L$ showed a longer PFS (12 versus 6 months, HR 1.92, IC 95% 1.314–2.800, $P = 0.001$). Furthermore, we observed that patients with $SIRI \geq 2.3 \times 10^9/L$ were more likely to benefit from mFOLFIRINOX therapy. Patients with an elevated SIRI treated with mFOLFIRINOX versus gemcitabine plus nab-paclitaxel and gemcitabine showed a clinically and statistically significant difference in median OS of 17 months compared to 6 and 4 months respectively ($p < 0.001$). Conversely, the difference was not clinically significant in the $SIRI < 2.3 \times 10^9/L$ subgroup: 15.9 months versus 16.5 and 16, respectively.

Conclusion: An elevated SIRI ($\geq 2.3 \times 10^9/L$) was an independent prognostic factor for patients with metastatic pancreatic cancer, warranting prospective evaluation.

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Introduction

Pancreatic ductal adenocarcinoma is the fourth cause of overall cancer-related death with 260,000 deaths annually, and has an overall 5-year survival rate of <5% in the metastatic setting [1]. The advanced stage of the disease at diagnosis, with more than 60% of

patients considered unresectable [2], is one of the main causes of its poor prognosis. Also, there is a lack of response to treatment associated with the existence of intrinsic (de novo) and extrinsic resistance (associated with current therapies) [3].

Metastatic pancreatic cancer patients survival has changed in the last decade, mainly due to new chemotherapeutic agents that have shown to be more effective than gemcitabine in monotherapy [4,5]. Chemotherapy regimens based on gemcitabine (gemcitabine plus nab-paclitaxel) [5] or FOLFIRINOX (fluorouracil, leucovorin, irinotecan and oxaliplatin) [4] have increased overall survival (OS)

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and both are approved as first line treatment in advanced disease. Prognostic factors in pancreatic cancer used to stratify the risk are tumor stage and tumor marker Cancer Antigen 19–9 (CA 19–9)⁶. In addition, we do not have predictive factors that allow us to select the optimal therapy. Nevertheless, recent work by Tiriác et al. [7] indicate that tumor transcriptomic signature may be the best way to select different chemotherapies.

In pancreatic cancer, in the same way as in other solid tumors, the role of the inflammatory and immune response to cancer has been widely studied [8]. In a study by Knoop RF et al. [9], with mouse models, it was found that tumor-associated macrophages, abundant in pancreatic cancer, can participate in resistance to gemcitabine. However, the relationship between the systemic inflammatory response and survival after chemotherapy has not been evaluated as a predictive factor in patients with pancreatic cancer.

Cancer-related inflammation has local and systemic consequences and represents a distinctive feature of the development and progression of neoplastic disease. From an immunological point of view, inflammation related to cancer is related to the local immune response in the tumor, which may precede and contribute to the development of cancer [10]. From a clinical point of view, it is a systemic reaction to the neoplasm, which results in a series of symptoms of systemic inflammation and is directly related to tumor staging and the clinical circumstances of the tumor [10]. Neutrophils are the first effectors of the acute systemic inflammatory response, followed by monocytes that are the ones that differentiate into macrophages in tumor tissue [11]. Circulating cytokines, acute phase proteins and circulating immune cells are responsible for the clinical symptoms that usually connote the presence and progression of cancer [12].

A systemic inflammation response index (SIRI) has been developed by Qi Qi et al. [13] based on peripheral neutrophil, monocyte, and lymphocyte counts. The aim of our study is to evaluate the prognostic value of SIRI in patients treated with gemcitabine plus nab-paclitaxel, FOLFIRINOX and gemcitabine. In this study, we evaluate in a larger cohort of patients if SIRI could be a predictive factor for mFOLFIRINOX treatment, as we had previously observed [14], in order to appropriately select patients who can benefit from more intensive therapies.

Methods

Patients and clinical specimens

This retrospective analysis included data from 164 patients who had pathologically confirmed metastatic pancreatic adenocarcinoma from 117 patients from Hospital Universitario La Princesa and 47 patients from McGill University Health Centre between January 2010 and January 2018. The criteria for metastatic disease corresponded to stage IV pancreatic cancer according to the International Union Against Cancer TNM Classification of Malignant Tumors (eighth edition) [15]. Contrast-enhanced abdominal computed tomography scans and/or magnetic resonance imaging were performed according to work-up guidelines [16] in all patients included in the study within the month before the start of treatment.

As per routine practice, the following data were collected in the institutional electronic medical records before treatment commencement: gender, age, ECOG PS, circulating tumor markers, routing hematology including full blood count. Patients with acute infectious diseases, including acute pancreatitis, cholangitis, or other active concomitant infections, within the past month were excluded all of the analyses, as in previous studies [13]. Treatment decisions were based on clinical and radiographic grounds, and not on serum CA 19–9 or SIRI values.

As per internal guidelines, the preferred regimen for patients with ECOG PS 0 was combination therapy. However, in some cases, the gemcitabine regimen was adopted with main reasons for withdrawing combination therapy being 1) patient's preference or 2) pre-existent peripheral neuropathy that could worsen with nab-paclitaxel or oxaliplatin treatment. All patients had a computed tomography scan performed at baseline, prior to the start of treatment. Treatment was continued until unacceptable toxicity, progression of disease or request of termination by individual patients. Tumor progression assessment was performed approximately every 8 weeks according to the Response Evaluation Criteria in Solid Tumors (RECIST) [17].

The laboratory data including neutrophil, lymphocyte, levels of tumor marker CA 19–9 were obtained by pre-treatment exploration 1 week-1 day prior to initiating chemotherapy treatment. The upper limit of normal in the laboratory for CA 19–9 ranged from 2 to 30 U/mL. The Neutrophil/Lymphocyte Ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count; an NLR ≥ 5 was considered elevated on the basis of previous studies [18]. Patient's surveillance during treatment included routine clinical and laboratory examination and imaging methods.

The SIRI

The SIRI was defined as follows: $SIRI = N \times M/L$, where N, M and L are the pretreatment peripheral neutrophil, monocyte and lymphocyte counts, respectively, as previously described [13,14]. The optimal SIRI cutoff values for tumor progression after chemotherapy in the training cohort were calculated with an ROC analysis. The Youden index (sensitivity + specificity – 1) was used to select a threshold to estimate sensitivity and specificity. The results of the ROC analysis revealed an optimal SIRI cutoff point of $2.3 \times 10^9/L$.

Statistical analysis

Our primary endpoint was to evaluate the predictive value of baseline SIRI for OS. OS was defined as the interval between the beginning of chemotherapy treatment and death; for patients who had not died at last follow-up, OS was censored to last follow-up. The secondary endpoint was the association between SIRI and progression-free survival (PFS), defined as the period beginning on the date of treatment commencement and ending with the first observation of disease progression [17], if a patient had not reached the progression endpoint, PFS was censored at the time of last follow-up. Another secondary endpoint was the association between known prognostic factors in metastatic pancreatic cancer, such as CA 19–9 and NLR, and OS.

Associations between variables were assessed with Pearson chi-square tests. All variables with a prognostic value $p < 0.3$ in univariate analysis were selected for further evaluation in the final multivariate Cox proportional-hazard model to determine whether the SIRI was an independent prognostic indicator of OS and PFS. In the multivariate Cox-regression analysis, the enter method was used to enter independent variables into the model.

Clinical endpoints were calculated using the Kaplan-Meier method and compared by the log-rank test. All statistical analyses were performed using the Statistical Package for Social Sciences version 22.0 (SPSS Inc., Chicago IL, USA). A two-sided $p < 0.05$ was considered statistically significant.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2008. The local ethics committee and Institutional Review Board of both institutions approved the study.

Results

Patient characteristics and clinical features

In total 164 patients were included in the study. The median age at baseline was 66 years (57.5–74). Patients were treated with mFOLFIRINOX (fluorouracil 2400 mg/m², leucovorin 400 mg/m², irinotecan 180 mg/m² and oxaliplatin 85 mg/m² doses every 2 weeks) (n = 22), gemcitabine plus nab-paclitaxel (gemcitabine 1000mg/m² plus nab-paclitaxel 100mg/m² weekly on days 1, 8 and 15 every 4 weeks) (n = 59), gemcitabine (gemcitabine 1000 mg/m² weekly on days 1, 8 and 15 every 4 weeks) (n = 40), folfox (fluoracil 2400 mg/m², leucovorin 400 mg/m² and oxaliplatin 85 mg/m² doses every 2 weeks) (n = 4) or gemcitabine + erlotinib (n = 9) as per protocol for at least two cycles. 30 patients included in the study had not received treatment (Table 1).

We observed an imbalance in ECOG PS between patients receiving combination therapy: 91% of patients who received mFOLFIRINOX and 54% of patients who received gemcitabine plus nab-paclitaxel showed an ECOG PS 0 compared to 57% of patients who received gemcitabine that had an ECOG PS of 1 ($P < 0.0001$). Patients with comorbidities were less likely to receive treatment ($P = 0.039$). The majority of patients who received combination therapy had liver metastases in comparison to the group of patients who received gemcitabine that had an equal distribution between liver and extrahepatic metastases ($P = 0.003$).

Prognostic value of SIRI

In the ROC analysis comparing the sensitivity and specificity of predicting survival, the SIRI (area under de curve (AUC) at 6 months: 0.777) was a better predictor of survival than CA 19–9 (AUC at 12 months: 0.676) or NLR (AUC at 6 months: 0.743) (Fig. 1). SIRI was confirmed to be a biomarker significantly associated with OS in the whole study cohort, with median OS of 16 months and 4.8 months ($P < 0.001$) for patients with SIRI $< 2.3 \times 10^9/L$ and SIRI $\geq 2.3 \times 10^9/L$ respectively (Fig. 2), Hazard Ratio (HR) 2.87, [Confidence Interval (CI) 95% 2.02–4.07], $P < 0.0001$. In addition, SIRI showed prognostic power with regard to PFS: median PFS 12 and 6 months, respectively, HR 1.92 (CI95% 1.31–2.80), $p = 0.001$.

The median survival time of all patients included was 11.8

months. The median OS corresponding to the main chemotherapy regimens (Fig. 3A) for patients who received mFOLFIRINOX was 16.8 months, for gemcitabine plus nab-paclitaxel was 14.4 months and for gemcitabine was 9 months ($P = 0.462$). Univariate analysis for predicting OS (Table 2) indicated that age, ECOG PS, comorbidities [19], chemotherapy treatment, biliary stent, NLR ≥ 4 and SIRI $\geq 2.3 \times 10^9/L$ had a statistically significant association with OS; whereas gender, cigarette and alcohol consumption, tumor and nodal staging, location and CA 19–9 ≥ 37 U/mL had no prognostic significance for OS. Subsequent multivariate analyses (Table 3) confirmed that SIRI was an independent prognostic factor for OS.

The median PFS (Fig. 3B) for patients who received mFOLFIRINOX was 9.1 months, for gemcitabine plus nab-paclitaxel was 9.9 months and for gemcitabine was 7.3 months, these differences were clinically but not statistically significant ($P = 0.818$). Univariate analysis for predicting PFS (Table 2) indicated that ECOG PS, tumor stage, chemotherapy treatment, biliary stent, CA 19–9 ≥ 37 U/mL, NLR and SIRI had a statistically significant association with PFS; but gender, age, comorbidities [19], cigarette and alcohol consumption, nodal staging and location had no prognostic significance for PFS. Subsequent multivariate analyses (Table 3) confirmed that SIRI was an independent prognostic factor for PFS.

SIRI and other prognostic factors

At univariate analysis, SIRI was confirmed to be significantly associated with survival, with an 87% increased risk of death per 2-unit increase in SIRI, HR 2.87, 95% CI 2.022–4.075, $P < 0.0001$ (Table 2). Age, ECOG PS, comorbidities, biliary stent, NLR ≥ 4 and first line chemotherapy regimen also had a statistically significant association with OS. CA 19–9 showed no prognostic significance when evaluated with a cutoff value of 30 (normal range maximum). Among the selected factors included in the multivariate Cox-regression model, biliary stent, first line chemotherapy regimen and SIRI were independently associated with survival (Table 3).

For PFS, at univariate analysis, SIRI was confirmed to be significantly associated with progression with a HR 1.92, 95% CI 1.314–2.800, $P = 0.001$. ECOG PS, tumor stage, biliary stent, first line chemotherapy regimen, CA 19–9 when evaluated with a cutoff value of 30 (normal range maximum) and NLR had a statistically significant association with PFS as well. Among the factors selected

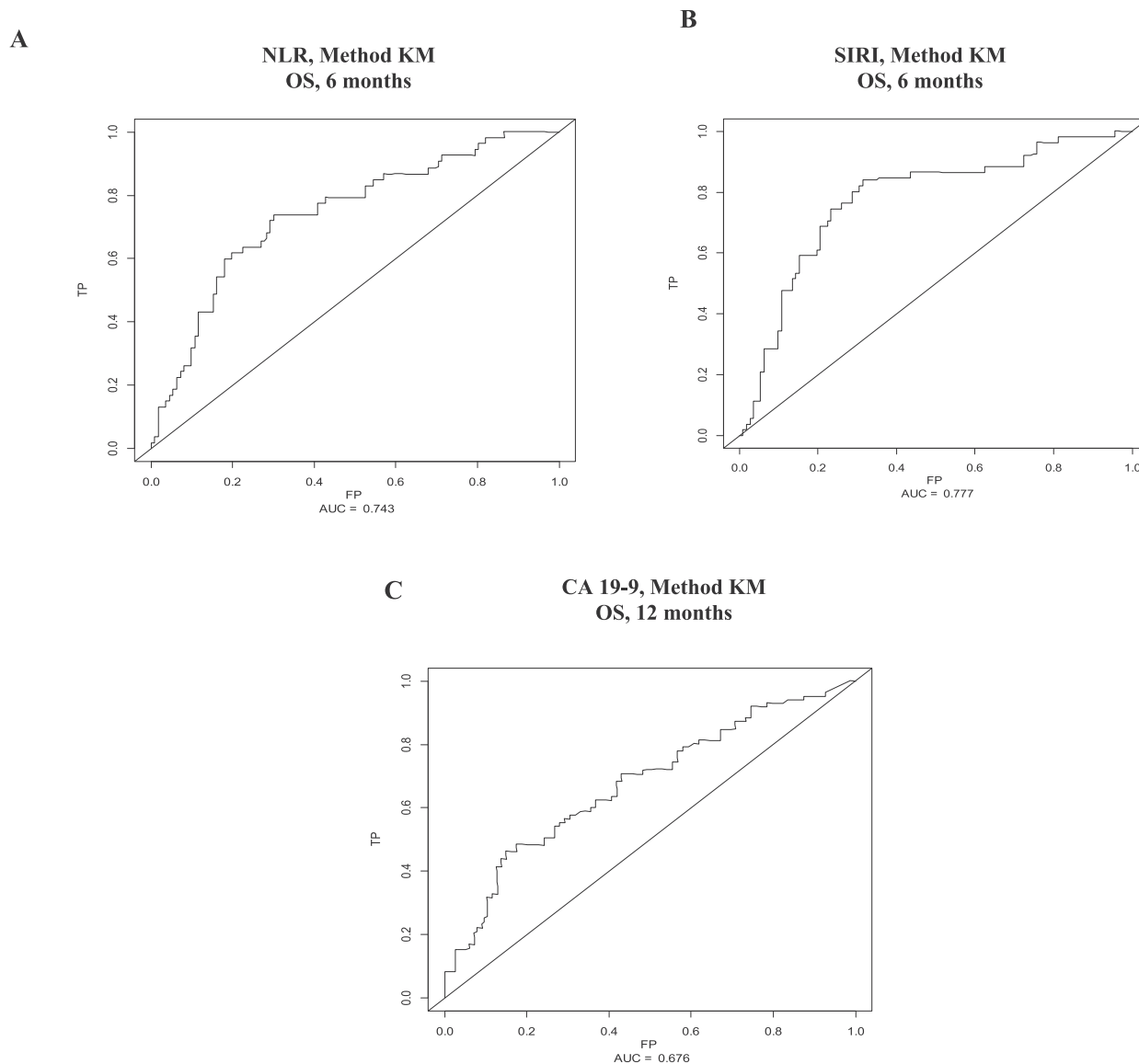
Table 1
Clinical characteristics of patients.

Variable	mFOLFIRINOX	Gemcitabine + Nab-Paclitaxel	Gemcitabine	Other regimens	No treatment	P-value
No. Patients	22	59	40	13	30	.38
Age, mean (range), y	55 (43–72)	66 (35–81)	71 (46–87)	60 (40–78)	71 (29–87)	.43
ECOG PS						<.0001*
• 0	20 (91)	32 (54)	17 (43)	4 (31)	4 (13)	
• ≥ 1	2 (9)	27 (46)	23 (57)	9 (69)	26 (87)	
Gender						.41
• Male	15 (68)	35 (59)	20 (50)	6 (46)	16 (53)	
• Female	7 (32)	24 (41)	20 (50)	7 (54)	14 (47)	
Comorbidities						.039*
• No	20 (91)	48 (81)	30 (75)	10 (77)	18 (60)	
• Yes	2 (9)	11 (41)	10 (25)	3 (23)	12 (40)	
Location						.664
• Head	13 (59)	34 (58)	28 (70)	12 (92)	12 (40)	
• Body-tail	9 (41)	25 (42)	12 (30)	1 (8)	18 (60)	
Location Metastases						.003*
• Only liver	14 (64)	24 (41)	17 (43)	5 (38)	7 (24)	
• Extrahepatic	6 (27)	16 (27)	18 (45)	6 (46)	10 (33)	
• Liver + other	2 (9)	19 (32)	5 (12)	2 (16)	13 (43)	
Median OS, mo	16	14	9	11	2	<.0001*

ECOG PS indicates Eastern Cooperative Oncology Group Performance Status.

Data presented as No. Patients (%) unless otherwise specified.

P value presented in **bold*** are statistically significant.



	Area Under the Curve			Cutoff Point	Sensitivity	Specificity	Youden Index
	6 months	12 months	24 months				
NLR	0.743	0.719	0.630	4	73.9%	69.9%	0.4378
SIRI	0.777	0.760	0.682	2.3	84.0%	68.64%	0.5260
CA199	0.617	0.676	0.621	5153.6	46.4%	85.2%	0.3155

Fig. 1. A comparison of the sensitivity and specificity of survival prediction by the Systemic Inflammatory Response Index (SIRI), Neutrophil Lymphocyte Ratio (NLR) and CA 19–9. This figure shows the Receiver Operating Curve (ROC) analysis to set the best NLR (A), SIRI (B) and CA 19–9 cutoff (C).

for multivariate analysis, first line chemotherapy, tumor stage, CA 19–9 and SIRI were independently associated with PFS.

Predictive value of SIRI for mFOLFIRINOX treatment

To evaluate if treatment efficacy was different in patients with a SIRI $< 2.3 \times 10^9/L$ and SIRI $\geq 2.3 \times 10^9/L$, we performed an analysis comparing the 6 subgroups defined by the three most used chemotherapy treatments used as first line (gemcitabine,

gemcitabine + nab-paclitaxel and mFOLFIRINOX) and an analysis by subgroups defined by SIRI. In the subgroup analysis defined by treatment, we observed differences between them. The most interesting finding is that when SIRI values were $< 2.3 \times 10^9/L$ there were no differences between treatment received; however, in the group of patients with SIRI $\geq 2.3 \times 10^9/L$ we observed a longer OS with mFOLFIRINOX therapy (Fig. 4A).

On the other hand, the subgroup analysis defined by SIRI values, we compared treatment outcomes for patients with SIRI $< 2.3 \times 10^9/L$

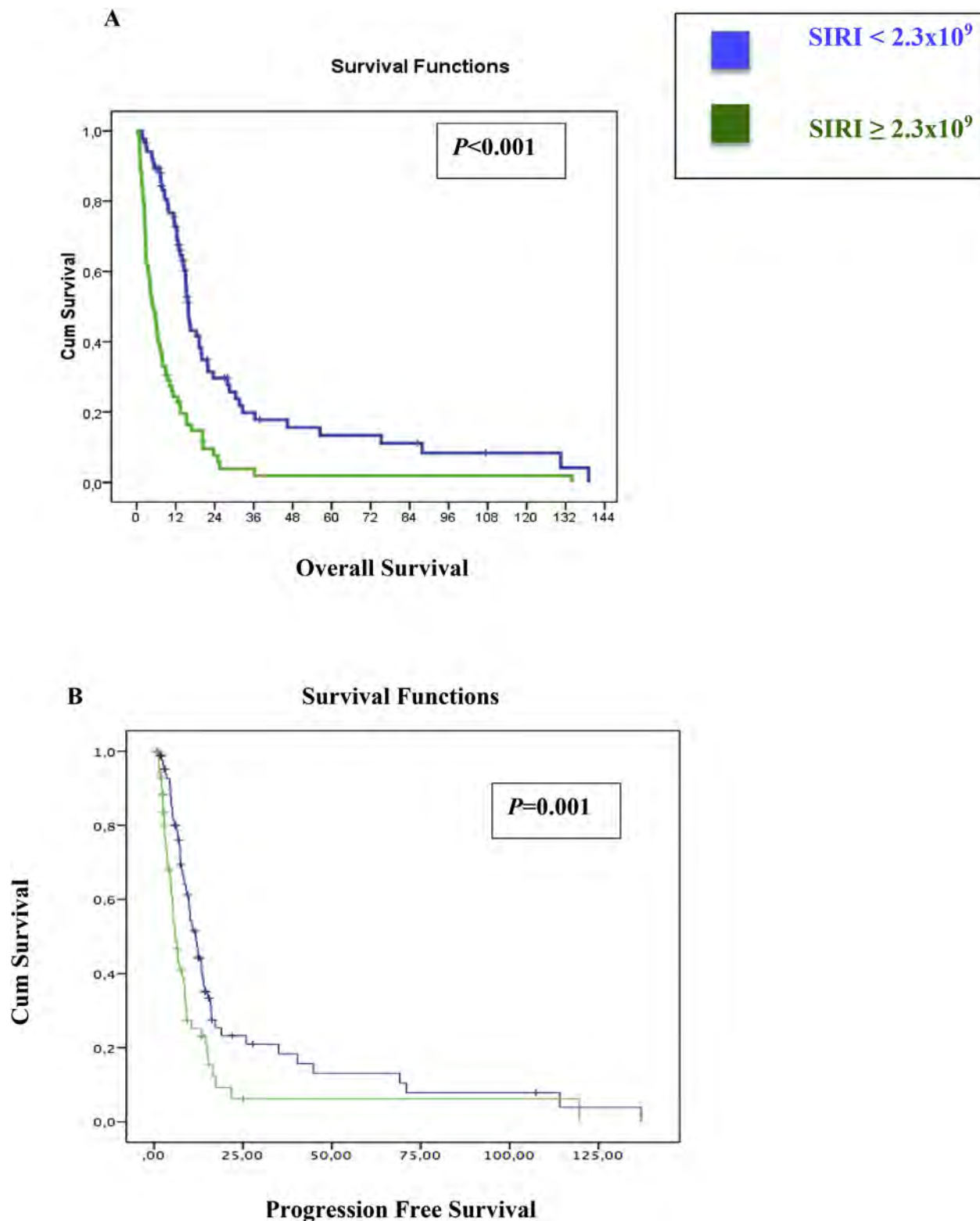


Fig. 2. **A.** Kaplan-Meier curves illustrate OS for the whole cohort of patients with metastatic pancreatic cancer who received chemotherapy treatment based on the systemic inflammation response index (SIRI) values. **B.** Kaplan-Meier curves illustrate PFS for the whole cohort of patients with metastatic pancreatic cancer who received chemotherapy treatment based on the SIRI values.

L and $SIRI \geq 2.3 \times 10^9/L$. We observed statistically significant differences between treatments for patients with $< 2.3 \times 10^9/L$, and the benefit of mFOLFIRINOX triplet was mostly confined to these patients (Fig. 4B).

In further confirmation of this, we made a subgroup analysis defined by CA 19-9 levels as related to tumor burden. We compared treatment outcomes for patients with CA 19-9 < 30 U/mL and for CA 19-9 ≥ 30 U/mL. On the contrary of what we observed with SIRI,

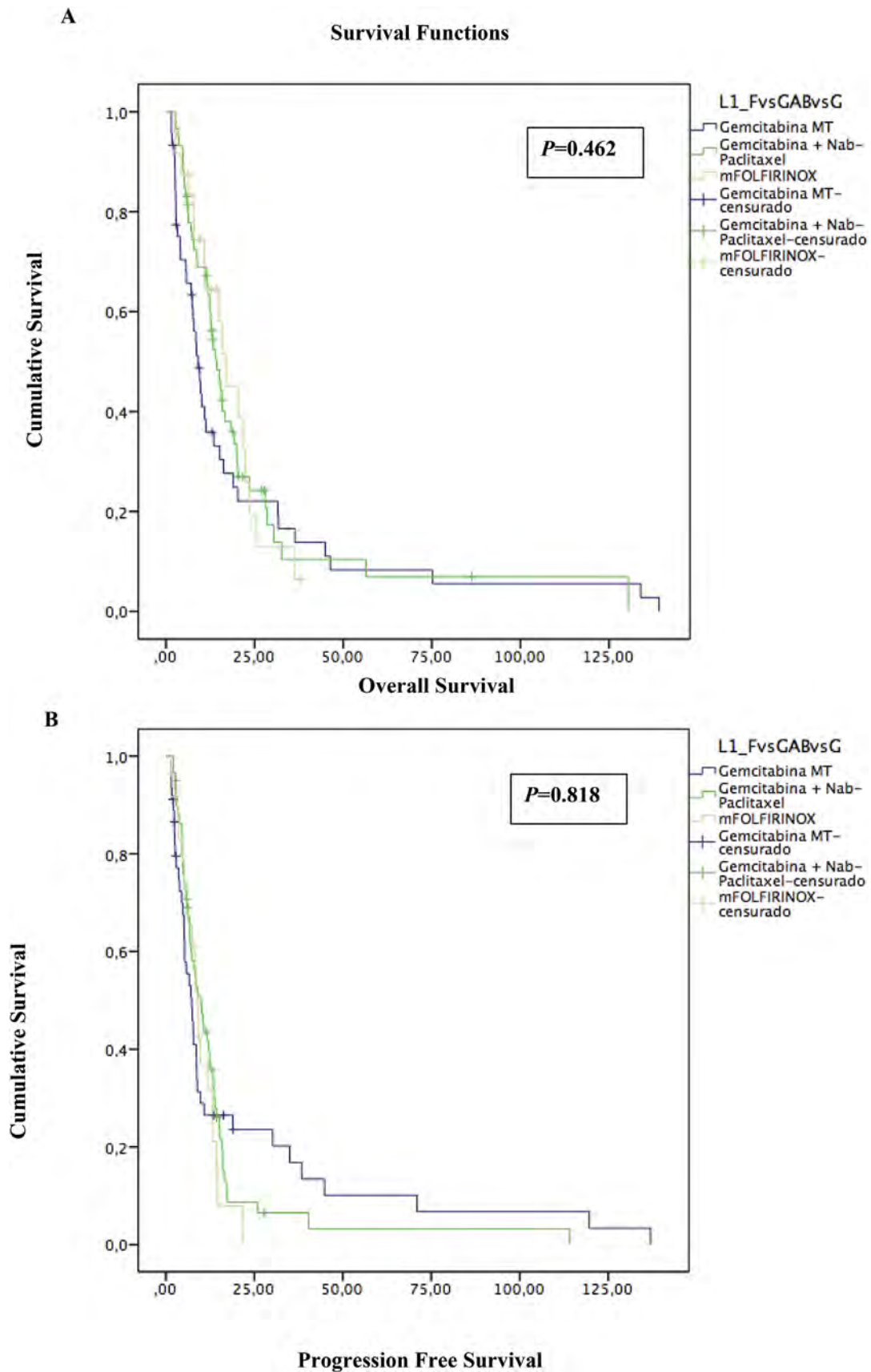


Fig. 3. **A.** Kaplan-Meier curves illustrate overall survival of patients with metastatic pancreatic cancer based on chemotherapy regimen. **B.** Kaplan-Meier curves illustrate progression free survival of metastatic pancreatic cancer patients based on chemotherapy regimen.

Table 2

Univariate analysis of the patients characteristics and the association with overall survival and progression free survival.

VARIABLE	Overall Survival				Progression Free Survival			
	Sig.	HR	Lower	Upper	Sig.	HR	Lower	Upper
Women	.347	.855	.616	1.186	.746	1.062	.740	1.524
Age	.007	1.021	1.006	1.037	.583	1.005	.988	1.022
ECOG PS	.004	1.641	1.173	2.296	.016	1.562	1.088	2.243
Comorbidities	.012	1.596	1.108	2.300	.288	1.263	.821	1.942
Cigarette ≥ 10 p/a	.223	1.266	.866	1.851	.879	.966	.618	1.508
Alcohol	.084	1.424	.953	2.128	.454	1.213	.732	2.009
cT3/T4	.889	.969	.625	1.503	.002	.501	.320	.784
cN1/2	.607	1.092	.781	1.527	.343	1.195	.826	1.729
Location Body/Tail	.133	1.286	.927	1.786	.322	1.204	.834	1.738
Biliary Stent	.000	2.084	1.440	3.015	.002	1.905	1.262	2.876
Chemotherapy	.000	.323	.216	.482	.000	.845	.768	.929
CA 19–9 ≥ 30 U/mL	.095	1.44	.939	2.193	.01	1.92	1.170	3.137
NLR ≥ 4	.000	2.59	1.819	3.690	.002	1.87	1.265	2.749
SIRI $\geq 2.3 \times 10^9$	.000	2.87	2.022	4.075	.001	1.92	1.314	2.800

Abbreviations: Sig: Significance. HR: Hazard Ratio. ECOG PS: Eastern Cooperative Oncology Group Performance Status. Comorbidities according to Charlson Index. cT3/T4: Tumor stage. cN1/2: Nodal stage. NLR: Neutrophil/Lymphocyte Ratio. SIRI: Systemic Inflammation Response Index.

Table 3

Multivariate analysis of the patients characteristics and the association with overall survival and progression free survival.

VARIABLE	Overall Survival				Progression Free Survival			
	Sig.	HR	Lower	Upper	Sig.	HR	Lower	Upper
ECOG PS	.524	1.16	.724	1.886	.163	1.28	.904	1.821
cT3/T4	.009	.72	.565	.923	.009	.72	.565	.923
Biliary Stent	.039	1.72	1.028	2.875	.051	1.69	.997	2.879
Chemotherapy	.000	.33	.187	.580	.016	.87	.781	.975
CA 19–9 ≥ 30 U/mL	.005	2.46	1.309	4.633	.005	2.46	1.309	4.633
SIRI $\geq 2.3 \times 10^9$	.000	3.95	2.467	6.303	.001	2.28	1.419	3.661

Abbreviations: Sig: Significance. HR: Hazard Ratio. ECOG PS: Eastern Cooperative Oncology Group Performance Status. cT3/T4: Tumor stage. SIRI: Systemic Inflammation Response Index.

patients with CA 19–9 ≥ 30 U/mL showed a benefit of combined chemotherapy regimens, without showing a confined benefit to mFOLFIRINOX or gemcitabine + nab-paclitaxel.

Discussion

Previously, we had observed that SIRI was the only index that was significantly associated with median OS in patients treated with FOLFIRINOX, gemcitabine plus nab-paclitaxel and gemcitabine alone when compared to NLR and CA19-9, but no prognostic significance for PFS [14]. In this study, SIRI was also significantly associated with median OS and PFS.

Patients in the mFOLFIRINOX cohort of our study showed a median OS of 16.8 months and median PFS of 9.1 months which is longer than in the ACCORD11 trial [4] (11 and 7 months respectively), mainly because the patients treated with mFOLFIRINOX in our study were most of them ECOG PS 0 and were younger than 71 years old. The median OS of 16.8 months was also longer than in our previous report (11.5 months) which can be related to a longer follow-up [14]. The cohort of patients treated with gemcitabine + nab-paclitaxel showed a median OS of 14.4 months in comparison to 8.5 months observed in the MPACT trial [5], and a median PFS of 9.9 months which is in accordance to the survival observed in a recent systematic review performed with real-world data [20]. The use of second line chemotherapy with novel therapies [21,22] could explain the longer OS of metastatic pancreatic cancer patients observed in our study.

The relationship between cancer and inflammation has been

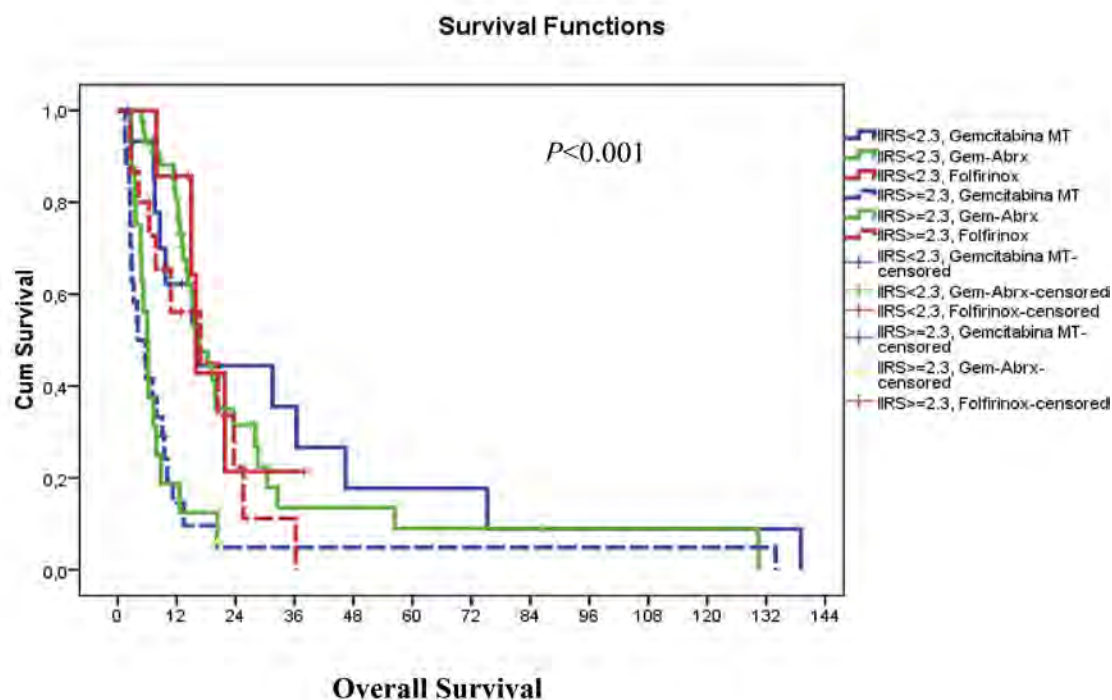
evaluated previously in pancreatic cancer [14,23–26]. Preoperative platelet-lymphocyte ratio was shown to be an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma in a study by Smith RA et al. [27]. The prognostic usefulness of circulating neutrophils is apparent as an independent measure or as part of the NLR in many types of cancer [13], but study results in the literature are controversial [28,29]. Also, C-reactive protein has shown to be significantly associated with survival (HR = 1.009, 95%CI 1.01–1.19, $P = 0.027$) in the ESPAC-4 phase III randomized adjuvant trial in resectable pancreatic cancer [30], but not the postoperative C-reactive protein (HR = 0.98, 95% CI = 0.93–1.04, $P = 0.577$); neither was significant on multivariate analysis. Of note, C-reactive protein is the major component of the modified Glasgow Prognostic Score mentioned by Jamieson et al. [28]. One of the strengths of our study is that was focused on patients with metastatic pancreatic cancer. Most of the studies that evaluated systemic inflammation response markers were performed with resectable tumors [18,29,31–33].

In unresectable tumors, acquiring sufficient tissue of pancreatic cancer can be difficult in order to identify biomarkers of prognostic and predictive utility. Therefore, SIRI was developed by Qi Qi et al. [13] in the clinical setting, providing a noninvasive, accessible and reproducible approach for predicting survival with advanced pancreatic cancer. In the Qi Qi et al. study [13] SIRI was confirmed to be a prognostic factor in pancreatic adenocarcinoma after gemcitabine-based chemotherapy in 1 prospective, randomized controlled trial of gemcitabine palliative chemotherapy for patients with advanced pancreatic cancer, but one of the main limitations was that patients with mFOLFIRINOX and gemcitabine + nab-paclitaxel were not included.

In our study, we were able to confirm SIRI was a prognostic factor in metastatic pancreatic cancer treated with mFOLFIRINOX, gemcitabine + nab-paclitaxel, gemcitabine alone, other regimens and also in patients who had not received chemotherapy; these results were in accordance to what we had observed in our previous study [14]. The prognostic ability was greater than that of the NLR and CA 19-9 levels when evaluated with ROC curves, as previously reported [13]. mFOLFIRINOX showed a longer OS and PFS in comparison to gemcitabine-based therapies, but these differences were not statistically significant, as observed in previous studies [20]. In the univariate and multivariate analysis, first line chemotherapy was significantly associated with longer OS, which is in accordance with the literature [4,5].

Univariate and multivariate analysis for predicting OS indicated

A



	Treatment	Time	Accumulated Events	Survival Function	95% Confidence Interval	
SIRI <2.3	mFOLFIRINOX	6 months	0			
		12 months	1	86%	33%	98%
		24 months	4	21%	1%	60%
	Gemcitabine + Nab-Paclitaxel	6 months	3	93%	80%	98%
		12 months	8	81%	65%	90%
		24 months	25	32%	17%	47%
	Gemcitabine	6 months	1	93%	61%	99%
		12 months	5	62%	31%	82%
		24 months	7	44%	17%	69%
SIRI ≥2.3	mFOLFIRINOX	6 months	3	80%	50%	93%
		12 months	6	56%	26%	78%
		24 months	9	22%	4%	51%
	Gemcitabine + Nab-Paclitaxel	6 months	8	50%	25%	71%
		12 months	13	19%	5%	40%
		24 months	15			
	Gemcitabine	6 months	14	42%	22%	60%
		12 months	20	15%	4%	32%
		24 months	22	5%	0%	20%

Fig. 4. A) Kaplan Meier curves comparing 6 subgroups defined by first line chemotherapy treatment. B) Kaplan Meier analysis comparing subgroups defined by SIRI values. **Abbreviations:** Sig: Significance. HR: Hazard Ratio. Ref: Reference.

	Treatment	N	%	Median	Lower Limit	Upper Limit
SIRI <2.3	mFOLFIRINOX	7	5.8	15,933	13,950	17,916
	Gemcitabine + Nab-Paclitaxel	43	35.5	16,567	12,388	20,746
	Gemcitabine	16	13.2	16,267	5,964	26,569
SIRI ≥2.3	mFOLFIRINOX	15	12.4	16,867	1,130	32,603
	Gemcitabine + Nab-Paclitaxel	16	13.2	6,000	4,105	7,895
	Gemcitabine	24	19.8	4,100	1,099	7,101

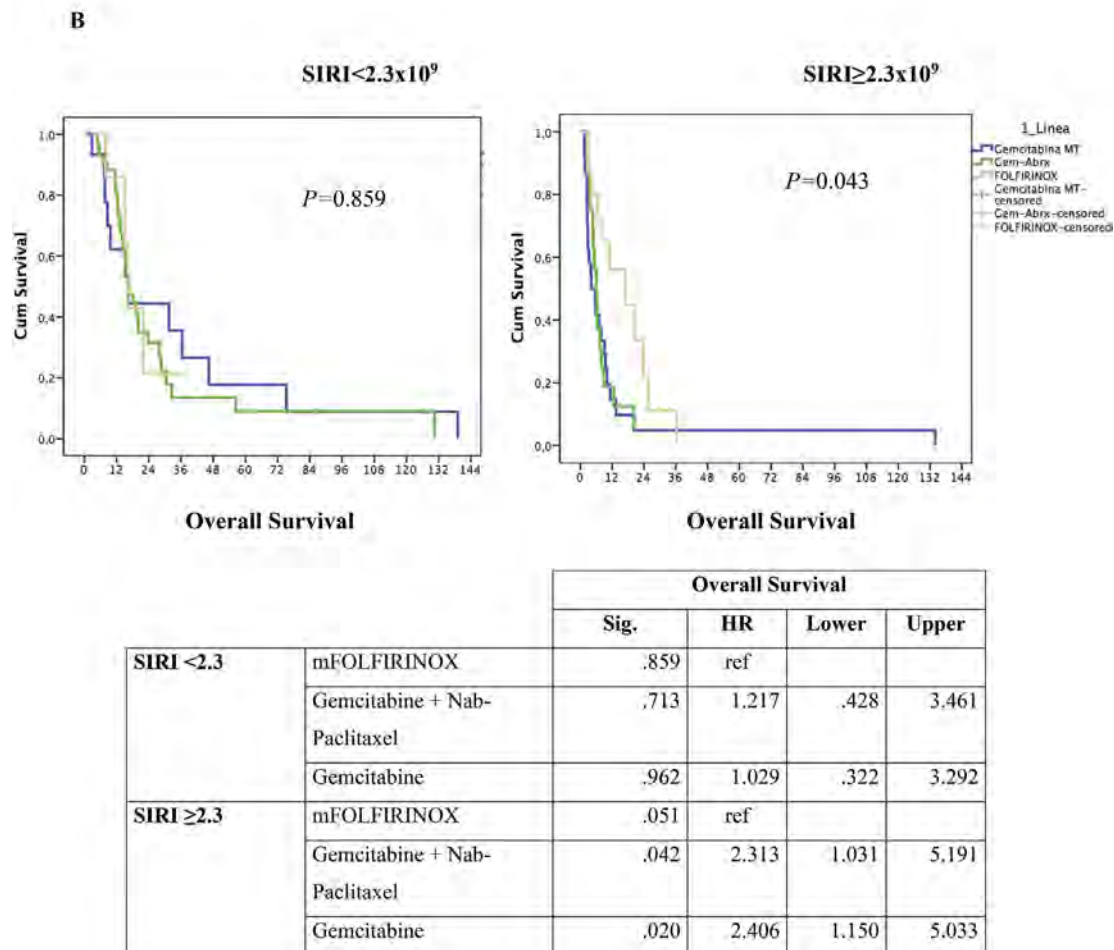


Fig. 4. (continued).

that $\text{SIRI} \geq 2.3 \times 10^9/\text{L}$ was associated with a shorter median OS. Furthermore, patients with $\text{SIRI} \geq 2.3 \times 10^9/\text{L}$ were more likely to benefit from mFOLFIRINOX therapy. Conversely, there was no difference observed in the $\text{SIRI} < 2.3 \times 10^9/\text{L}$ subgroup. In addition, we performed an analysis by subgroups defined by SIRI value where we observed that the benefit of mFOLFIRINOX triplet is mostly confined to $\text{SIRI} \geq 2.3 \times 10^9/\text{L}$, in accordance to our previous study [14]. In metastatic pancreatic cancer, CA19-9 levels are widely used for predicting prognosis of patients with advanced pancreatic cancer [6], but in our study no predictive value was observed.

Our study is retrospective and non-randomized, with several limitations including the potential for selection bias. Baseline

differences between mFOLFIRINOX, gemcitabine + nab-paclitaxel and gemcitabine alone may have biased our results. The differences observed in the potential clinical utility of SIRI for predicting outcome and response to mFOLFIRINOX might be explained by the different clinical and biochemical criteria that are required to select patients for mFOLFIRINOX. We attempted to control these differences with multivariate analysis; however, there are unmeasured differences that may have influenced our findings. Our mFOLFIRINOX group was small with 22 patients, and that could have underpowered our analysis. Another major limitation of our study is that the cut-off point for the SIRI was derived post-hoc; to be meaningful this would need to be tested in a second independent

cohort. SIRI values differ between studies due to the difference in sample size and the retrospective nature of the studies [13,14]. Nonetheless, to the best of our knowledge, this is the first study to show a significant predictive ability of SIRI in patients treated with mFOLFIRINOX in the real-world setting. Future prospective and controlled studies should determine the prognostic and predictive ability of SIRI.

Conclusion

An elevated SIRI ($\geq 2.3 \times 10^9/L$) was an independent prognostic factor for patients with metastatic pancreatic cancer, warranting prospective evaluation. The results of this study suggest that SIRI may be useful in appropriately selecting patients who would benefit of mFOLFIRINOX therapy as a more intensive first-line chemotherapy regimen.

Anatomic site

Metastatic Pancreatic Cancer.

Authors contribution

Vilma Pacheco-Barcia: The key person responsible for the article, who contributed to the conception and design of the study, data acquisition, statistical analysis, interpretation of the data and writing of the manuscript.

Talya France, Jamil Asselah and George Zogopoulos: Contributed to conception and design of the study, acquisition and interpretation of the data. Olga Donnay, Nathaniel Bouganin, Katie Guo, Jacobo Rogado, Elena Martin and Thierry Alcindor: Contributed to the acquisition of the data. Ramon Colomer contributed to the acquisition and interpretation of the data. Rebeca Mondejar: Contributed to the interpretation of the data. All authors reviewed and approved the final version of this manuscript.

Declaration of competing interest

The authors declare there are no conflicts of interests.

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References

- [1] Hariharan D, Saeed A, Kocher HM. Analysis of mortality rates for pancreatic cancer across the world. *HPB* 2008;10(1):58–62. <https://doi.org/10.1080/13651820701883148>.
- [2] Burris HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997;15(6):2403–13. <https://doi.org/10.1126/science.1198443>.
- [3] Kleeff J, Korc M, Apte M, et al. Pancreatic cancer. *Nat Rev Dis Prim* 2016;2(April):1–23. <https://doi.org/10.1038/nrdp.2016.22>.
- [4] Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364(19):1817–25. <https://doi.org/10.1056/NEJMoa1011923>.
- [5] Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013;369(18):1691–703. <https://doi.org/10.1056/NEJMoa1304369>.
- [6] Balleshaniina UK, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: an evidence based appraisal. *J Gastrointest Oncol* 2012;3(2):105–19. <https://doi.org/10.3978/j.issn.2078-6891.2011.021>.
- [7] Tiriak H, Belleau P, Engle DD, et al. Organoid profiling identifies common responders to chemotherapy in pancreatic cancer. *Cancer Discov* 2018. <https://doi.org/10.1158/2159-8290.CD-18-0349>.
- [8] Crozier JEM, McKee RF, McArdle CS, et al. The presence of a systemic inflammatory response predicts poorer survival in patients receiving adjuvant 5-FU chemotherapy following potentially curative resection for colorectal cancer. *Br J Canc* 2006;94(12):1833–6. <https://doi.org/10.1038/sj.bjc.6603185>.
- [9] Knoop RF, Sparrn M, Waldmann J, et al. Chronic pancreatitis and systemic inflammatory response syndrome prevent impact of chemotherapy with gemcitabine in a genetically engineered mouse model of pancreatic cancer. *Neoplasia* 2014;16(6):463–70. <https://doi.org/10.1016/j.neo.2014.05.010>.
- [10] Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. *Lancet Oncol* 2014;15(11):e493–503. [https://doi.org/10.1016/S1470-2045\(14\)70263-3](https://doi.org/10.1016/S1470-2045(14)70263-3).
- [11] Manuscript A, Coussens LM, Werb Z. Inflammation and cancer. *Nature* 2010;420(6917):860–7. <https://doi.org/10.1038/nature01322>.
- [12] Laird B, McMillan D, Fayers P, Fearon K, Kaasa S. The systemic inflammatory response and its relationship to pain and other symptoms in advanced cancer. *The Oncologist* 2010;15(suppl 1):11–2. <https://doi.org/10.1634/theoncologist.2010-S1-11>.
- [13] Qi Q, Zhuang L, Shen Y, et al. A novel systemic inflammation response index (SIRI) for predicting the survival of patients with pancreatic cancer after chemotherapy. *Cancer* 2016;122(14):2158–67. <https://doi.org/10.1002/cncr.30057>.
- [14] Pacheco-Barcia V, Mondéjar Solís R, France T, et al. A systemic inflammation response index could be a predictive factor for mFOLFIRINOX in metastatic pancreatic cancer. *Pancreas* 2019;48(5):e45–7.
- [15] Chun YS, Pawlik TM, Vauthey JN. 8th edition of the AJCC cancer staging manual: pancreas and hepatobiliary cancers. *Ann Surg Oncol* 2017;1–3.
- [16] Ryan D, Hong T. Pancreatic adenocarcinoma. *N Engl J Med* 2005;1039–49. <https://doi.org/10.1056/NEJMr1404198>.
- [17] Schwartz LH, Litière S, De Vries E, et al. Recist 1.1 - update and clarification: from the RECIST committee. *Eur J Cancer* 2016. <https://doi.org/10.1016/j.ejca.2016.03.081>.
- [18] Stotz M, Gerger A, Eisner F, et al. Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. *Br J Canc* 2013;109(2):416–21. <https://doi.org/10.1038/bjc.2013.332>.
- [19] Roffman CE, Buchanan J, Allison GT. Charlson comorbidities index. *J Physiother* 2016;62(3):171. <https://doi.org/10.1016/j.jphys.2016.05.008>.
- [20] Chiorean EG, Chung WY, Giordano G, Kim G, Al-Batran SE. Real-world comparative effectiveness of nab-paclitaxel plus gemcitabine versus FOLFIRINOX in advanced pancreatic cancer: a systematic review. *Ther Adv Med Oncol* 2019. <https://doi.org/10.1177/1758835919850367>.
- [21] Wang-Gillam A, Li CP, Bodoky G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. *Lancet* 2016. [https://doi.org/10.1016/S0140-6736\(16\)00986-1](https://doi.org/10.1016/S0140-6736(16)00986-1).
- [22] Grierson P, Lim KH, Amin M. Immunotherapy in gastrointestinal cancers. *J Gastrointest Oncol* 2017;8(3):474–84. <https://doi.org/10.21037/jgo.2017.05.01>.
- [23] Garcea G, Ladwa N, Neal CP, Metcalfe MS, Dennison AR, Berry DP. Preoperative neutrophil-to-lymphocyte ratio (NLR) is associated with reduced disease-free survival following curative resection of pancreatic adenocarcinoma. *World J Surg* 2011;35(4):868–72. <https://doi.org/10.1007/s00268-011-0984-z>.
- [24] Imtiaz F, Shafique K, Mirza S, Ayoob Z, Vart P, Rao S. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. *Int Arch Med* 2012;5(1):2. <https://doi.org/10.1186/1755-7682-5-2>.
- [25] Xiao Y, Xie Z, Shao Z, et al. Prognostic value of postdiagnostic inflammation-based scores in short-term overall survival of advanced pancreatic ductal adenocarcinoma patients. doi:10.1097/MD.00000000000009247
- [26] Ahn KS, Hwang JY, Han HS, Kim ST, Hwang I, Chun YO. The impact of acute inflammation on progression and metastasis in pancreatic cancer animal model. *Surg Oncol* 2018. <https://doi.org/10.1016/j.suronc.2017.11.008>.
- [27] Smith RA, Bosonnet L, Raraty M, et al. Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. *Am J Surg* 2009. <https://doi.org/10.1016/j.amjsurg.2007.12.057>.
- [28] Jamieson NB, Denley SM, Logue J, et al. A prospective comparison of the prognostic value of tumor- and patient-related factors in patients undergoing potentially curative surgery for pancreatic ductal adenocarcinoma. *Ann Surg Oncol* 2011;18(8):2318–28. <https://doi.org/10.1245/s10434-011-1560-3>.
- [29] Clark EJ, Connor S, Taylor MA, Madhavan KK, Garden OJ, Parks RW. Preoperative lymphocyte count as a prognostic factor in resected pancreatic ductal adenocarcinoma. *HPB* 2007;9(6):456–60. <https://doi.org/10.1080/13651820701774891>.
- [30] Neoptolemos JP, Palmer DH, Ghanah P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet* 2017. [https://doi.org/10.1016/S0140-6736\(16\)32409-6](https://doi.org/10.1016/S0140-6736(16)32409-6).
- [31] SOHN T, YEO C, CAMERON J, et al. Resected adenocarcinoma of the pancreas? 616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg* 2000;4(6):567–79. [https://doi.org/10.1016/S1091-255X\(00\)80105-5](https://doi.org/10.1016/S1091-255X(00)80105-5).

- [32] Tessier-Cloutier B, Kalloger SE, Al-Kandari M, et al. Programmed cell death ligand 1 cut-point is associated with reduced disease specific survival in resected pancreatic ductal adenocarcinoma. *BMC Canc* 2017;17(1):1–10. <https://doi.org/10.1186/s12885-017-3634-5>.
- [33] Shirai Y, Shiba H, Sakamoto T, et al. Preoperative platelet to lymphocyte ratio predicts outcome of patients with pancreatic ductal adenocarcinoma after pancreatic resection. *Surgery (St Louis)* 2015;158(2):360–5. <https://doi.org/10.1016/j.surg.2015.03.043>.

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362 0 a| Vol. 1/1 (May 1986)-v. 29, no. 3 (2001).

500 a| Published: Totowa, NJ, -2001.

538 a| Mode of access: World Wide Web.

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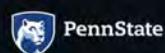
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Appendix PEDDI02

ORIGINAL ARTICLE

Multi-Institutional Experience with FOLFIRINOX in Pancreatic Adenocarcinoma

Parvin F Peddi¹, Sam Lubner⁵, Robert McWilliams⁶, Benjamin R Tan¹,
Joel Picus¹, Steven M Sorscher¹, Rama Suresh¹, A Craig Lockhart¹, Jian Wang⁷,
Christine Menias², Feng Gao³, David Linehan⁴, Andrea Wang-Gillam¹

¹Division of Medical Oncology, Department of Medicine, ²Division of Diagnostic Radiology, Mallinckrodt Institute of Radiology, ³Division of Biostatistics, and ⁴Section of Hepatobiliary and Pancreatic Surgery, Division of General Surgery; Washington University School of Medicine. Saint Louis, MO, USA. ⁵Division of Medical Oncology, Department of Medicine, University of Wisconsin School of Medicine and Public Health. Madison, WI, USA. ⁶Division of Medical Oncology, Mayo Clinic. Rochester, MN, USA. ⁷Division of Oncology, The Second Affiliated Hospital of Zhengzhou University. Zhengzhou, Henan, China

ABSTRACT

Context Combination chemotherapy with FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil, and leucovorin) was shown to be effective in a large phase III trial. **Objective** The purpose of this study was to examine the tolerance and effectiveness of FOLFIRINOX as practiced outside of the confines of a clinical trial and to document any dose modifications used by practicing oncologists. **Methods** Data on patients with all stages of pancreatic adenocarcinoma treated with FOLFIRINOX at three institutions was analyzed for efficacy, tolerance, and use of any dose modifications. **Results** Total of 61 patients was included in this review. Median age was 58 years (range: 37 to 72 years), 33 were male (54.1%) and majority had ECOG performance of 0 or 1 (86.9%, 53 patients). Thirty-eight (62.3%) had metastatic disease, while 23 (37.7%) were treated for locally advanced or borderline resectable disease. Patients were treated with a median number of four cycles of FOLFIRINOX, with dose modifications in 58.3% (176/302) of all cycles. Ten patients had stable disease (16.4%), four had a partial response (6.6%) while eight had progressive disease (13.1%) on best imaging following therapy. Median progression-free survival and overall survival were 7.5 months and 13.5 months, respectively. The most common grade 3-4 adverse event was neutropenia at 19.7% (12 cases), with 4.9% (3 cases) rate of febrile neutropenia. Twenty-one patients (34.4%) were hospitalized as a result of therapy but there were no therapy-related deaths. Twenty-three (37.7%) had therapy eventually discontinued as a result of adverse events. **Conclusion** Despite substantial rates of adverse events and use of dose modifications, FOLFIRINOX was found to be clinically effective in both metastatic and non-metastatic patients. Regimen toxicity did not detract from overall response and survival.

INTRODUCTION

Received June 7th, 2012 - Accepted July 10th, 2012

Key words Adenocarcinoma; Adult; Antimetabolites, Antineoplastic /adverse effects; Antineoplastic Combined Chemotherapy Protocols /adverse effects; Follow-Up Studies; Granulocyte Colony-Stimulating Factor; Neoadjuvant Therapy; Pancreatic Neoplasms; Registries; Survival Analysis; United States

Abbreviations ACCORD 11/PRODIGE 4: Action to Control Cardiovascular Risk in Diabetes 11/Partenariat de Recherche en Oncologie Digestive 4; ECOG: Eastern Cooperative Oncology Group; FOLFIRINOX: oxaliplatin, irinotecan, fluorouracil, and leucovorin; FOLFOX: oxaliplatin, fluorouracil, and leucovorin; G-CSF: granulocyte colony stimulating factor

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Pancreatic cancer remains the fourth leading cause of cancer death in the U.S. with an estimated 37,390 deaths in 2012 [1]. Progress in combating this malignancy has been slow with five year overall survival improving from 3% in 1970s to merely 6% in the early 2000s [1]. Until recently, the only chemotherapy shown to provide a modest survival benefit had been gemcitabine, which improved median overall survival from 4.4 to 5.6 months when compared to fluorouracil in a landmark phase III study [2]. Attempts at improving survival with combination of gemcitabine and a variety of cytotoxic and molecularly targeted agents have failed to provide substantial additional benefit [3, 4, 5]. Addition of erlotinib to gemcitabine was the only combination to provide a modest additional survival benefit of 6% at 1 year, resulting in an FDA approval for this agent [6]. In May 2011, Conroy *et al.* published the results of the Action to Control Cardiovascular Risk in Diabetes 11 /

Partenarait de Recherche en Oncologie Digestive 4 (ACCORD 11/PRODIGE 4) trial on FOLFIRINOX, as the first regimen to improve the median overall survival of patients with metastatic pancreatic cancer beyond 10 months [7]. FOLFIRINOX, consisting of a biweekly regimen of oxaliplatin, irinotecan, fluorouracil, and leucovorin, was compared in a phase II to III converted trial with gemcitabine in 342 patients in various European centers. Median overall survival was 11.1 months compared with 6.8 months in the gemcitabine group. Furthermore, in spite of higher rates of adverse events, patients in the FOLFIRINOX group reported a higher quality of life.

In spite of the improvement in survival, however, acceptance of FOLFIRINOX has been tempered with toxicity concerns of this potent regimen. A similar regimen (FOLFOXIRI: irinotecan 165 mg/m² day 1 instead of 180 mg/m² in FOLFIRINOX, same dose of oxaliplatin at 85 mg/m² day 1, leucovorin at 200 mg/m² day 1, and fluorouracil at 3,200 mg/m² 48-hour continuous infusion instead of 2,400 mg/m² in FOLFIRINOX) was tried in colon cancer and has not been widely accepted partly due to similar toxicity concerns [8]. We therefore sought to document the use of FOLFIRINOX and its efficacy and tolerance in patients treated at three U.S. academic institutions within the framework of a registry study.

MATERIALS AND METHODS

Patient Population

Patients with pancreatic adenocarcinoma at Washington University in St. Louis Siteman Cancer Center, Mayo Clinic, and University of Wisconsin Carbone Cancer Center, who were treated with FOLFIRINOX between January 2009 and April 2012, were eligible for inclusion. A retrospective and prospective registry was established to capture all patients after Institutional Board Review (IRB) approval was obtained at each institution. Patients were 18 years of age or older and had pathologically confirmed pancreatic adenocarcinoma. Treatment with at least one cycle of a regimen consisting of 5-fluorouracil, oxaliplatin, and irinotecan was required for entry into the registry. Patients with all stages of pancreatic cancer and prior treatment histories were eligible. Demographic data collected included age, race, gender, Eastern Cooperative Oncology Group (ECOG) performance status, stage at initiation of FOLFIRINOX, and any prior treatments. Baseline laboratory values were recorded including tumor marker CA 19-9. Data collection was stopped in March 2012.

Drug Administration

The standard FOLFIRINOX regimen has been previously described in the ACCORD 11 trial [7], consisting of oxaliplatin at 85 mg/m², leucovorin at 400 mg/m², irinotecan at 180 mg/m², and fluorouracil at 400 mg/m², followed by a continuous fluorouracil intravenous infusion of 2,400 mg/m² over a 46-hour

period every 2 weeks. Any deviation from this regimen, whether in the first or subsequent cycles, was recorded. The use of granulocyte colony stimulating factor (G-CSF) support, given to prevent or decrease levels of neutropenia, was recorded for each cycle. Patients were followed until cessation of FOLFIRINOX per the treating oncologist. The total number of cycles received was recorded.

Evaluation of Clinical Toxicity

All clinic notes were reviewed for any hospitalizations, dose reductions or cessation of treatment due to adverse events. Laboratory values before and after each treatment cycle were also reviewed to corroborate and document any additional adverse events using complete blood count and comprehensive metabolic panel in each patient. Adverse events were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, version 3.0) [9]. Most common adverse events specifically tabulated in the paper include neutropenia, neutropenic fever, thrombocytopenia, anemia, fatigue, nausea, abdominal pain, and diarrhea. Patients who received at least one cycle of chemotherapy were included for toxicity evaluation.

Assessment of Clinical Benefit

Staging imaging (CT or MRI) was obtained per the discretion of treating oncologists during treatment. These images were analyzed according to the Response Evaluation Criteria in Solid Tumors (RECIST) as described in the supplement of the ACCORD trial to determine response [7]. Images were included in response analysis if patients had received at least three cycles of a standard or modified FOLFIRINOX regimen prior to image acquisition. Original report by radiology was used for patients treated at Mayo Clinic and University of Wisconsin. An independent radiologist reviewed images of patients at Washington University, for the purposes of this study. Best response imaging was used for the purpose of determining clinical benefit. Clinic notes were also reviewed for clinician assessment of response and when it differed from radiological assessment, the clinical assessment of response was used.

ETHICS

Institutional Board Review (IRB) approval was obtained at each institution. Written or oral informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the "World Medical Association (WMA) Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects" adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the 59th WMA General Assembly, Seoul, South Korea, October 2008.

STATISTICS

Data analysis for this study was descriptive in nature. Demographic and clinical characteristics, as well as

Table 1. Characteristics of 61 patients with pancreatic adenocarcinoma treated with FOLFIRINOX between January 2009 and April 2012.

Institution:	
- Washington University	31 (50.8%)
- Mayo Clinic	12 (19.7%)
- University of Wisconsin	18 (29.5%)
Age (year):	
- Median	58
- Range	37-72
Gender:	
- Male	33 (54.1%)
- Female	28 (45.9%)
Ethnicity:	
- White	56 (91.8%)
- African Americans	5 (8.2%)
ECOG performance status:	
- 0-1	53 (86.9%)
- 2 or unknown	8 (13.1%)
Tumor location:	
- Head	25 (41.0%)
- Other locations or resected	36 (59.0%)
Biliary stent	17 (27.9%)
Stage:	
- Metastatic	38 (62.3%)
- Locally advanced	19 (31.1%)
- Borderline resectable	4 (6.6%)

adverse events and follow-up time were summarized using means, medians, and standard deviations, ranges or counts and frequencies as appropriate. Progression-free survival was defined as time of FOLFIRINOX initiation to time of progression based on imaging/clinical evaluation, or time of death, whichever occurred first. Those patients alive and progression-free were censored on March 1st, 2012, the date of data collection close. Overall survival was defined as time of FOLFIRINOX initiation to time of death. When not noted in clinical records, the Social Security Death index was used to ascertain survival and patients alive were censored in March 2012. The overall and progression-free survival were calculated using Kaplan-Meier product limit methods. Statistical analyses were performed using SAS (SAS Institutes, Cary, NC, USA).

RESULTS

Patients

Patient characteristics are shown in Table 1. A total of 61 patients were enrolled and followed for a median of 8.5 months (range of 1.5 to 20.4 months). Median age was 58 with a range of 37 to 72 years. Majority of the patients were male (54.1%), white (91.8%) and with ECOG performance of 0 or 1 (86.9%). Thirty-eight (62.3%) patients were treated for metastatic or recurrent disease, while 19 (31.1%) had locally advanced cancer and 4 had border-line resectable disease (6.6%). Twenty-five patients (41.0%) had tumor present in the pancreatic head at time of receiving FOLFIRINOX with 17 patients (27.9%) having a biliary stent.

Treatment

Patients received a median of 4 cycles of FOLFIRINOX with range of 1 to 22 cycles. Average number of cycles was 5.4. Three patients started with one cycle of FOLFOX (same dosage and schedule of oxaliplatin, 5-FU, and leucovorin as FOLFIRINOX, but omitting irinotecan) to test tolerability before the addition of irinotecan. This first cycle of FOLFOX was not counted towards cycle count or analysis.

The FOLFIRINOX regimen was modified in 31 patients (50.8%) empirically starting with the first cycle. Deletion of 5-FU and dose reduction of irinotecan were the most common modifications and were each selected for 22 patients with some overlap of the two groups. Thirty-two patients had UGT1A1 status evaluated and dose reduction of irinotecan was done in 4 patients due to presence of UGT1A1*28/28 genotype. Median dose intensities for the first cycle for each of the components were 100%. Average dose intensities for the first cycle for oxaliplatin, irinotecan, 5-FU bolus, and 5-FU continuous infusion were 98%, 90%, 59%, 99%, respectively. Overall dose averages for oxaliplatin, irinotecan, 5-FU bolus, and 5-FU continuous infusion were 96%, 88%, 57%, and 96%, respectively. From the 31 patients who started with full dose FOLFIRINOX, 20 (64.5%) required eventual dose reduction or discontinuation of therapy due to adverse events.

G-CSF support was included for 41 patients (67.2%) starting with the first cycle using filgrastim. Except for three patients in whom G-CSF support was later discontinued, all others were continued on G-CSF for all subsequent cycles. On the other hand, from the twenty patients who were not started on G-CSF with first cycle, 6 (30.0%) had G-CSF support added later on. Overall 47 patients (77.0%) received G-CSF support at some point in their therapy.

Adverse Events

There were no deaths as a result of therapy. In six patients (9.8%) treatment was stopped after the first cycle due to adverse events. Rates of the most common grade 3-4 adverse events are listed in Table 2. Neutropenia was the most common grade 3-4 adverse event, occurring in 12 patients (19.7%), while neutropenic fever occurred in three patients (4.9%).

Table 2. Severe adverse events observed in 61 patients with pancreatic adenocarcinoma treated with FOLFIRINOX.

Hematologic:	
- Neutropenia	12 (19.7%)
- Febrile neutropenia	3 (4.9%)
- Thrombocytopenia	2 (3.3%)
Non-hematologic:	
- Abdominal pain	5 (8.2%)
- Fatigue	3 (4.9%)
- Diarrhea	2 (3.3%)
Other grade 3-4 adverse events	7 (11.5%)
Hospitalization	21 (34.4%)

Table 3. Reason for discontinuation of therapy reported by 61 patients with pancreatic adenocarcinoma treated with FOLFIRINOX.

Adverse events	23 (37.7%)
Disease progression	18 (29.5%)
Resection	8 (13.1%)
Other reasons/Ongoing	12 (19.7%)

Two of these patients were already on G-CSF prophylaxis but were on full dose FOLFIRINOX therapy. Grade 3 or worse thrombocytopenia occurred in two patients (3.3%) while no patient had a grade 3-4 anemia. Abdominal pain, fatigue and diarrhea were the severe non-hematological adverse events that were observed. Intravenous fluids and anti-diarrhea medications as outpatient usually sufficed for treatment but hospitalizations were required for a total of 21 patients (34.4%). There was one case of cholangitis whose tumor was in the pancreatic head and did not have a stent. No definite correlation was observed between adverse events and UGT1A1 genotype.

Adverse events caused dose reduction in 23 patients (37.7%) and resulted in the eventual reason for discontinuation of FOLFIRINOX in 23 patients (37.7%). Overall eleven patients (18.0%) received full dose FOLFIRINOX throughout their treatment without adverse events necessitating dose reduction or cessation. Reason for eventual discontinuation of FOLFIRINOX therapy is depicted in Table 3.

Clinical Outcome

Forty patients (65.6%) had imaging available after at least three cycles of FOLFIRINOX therapy: 22 with metastatic disease (57.9%) and 18 with non-metastatic disease (78.3%). Overall, one patient had complete response (2.5%), nine patients had a partial response (22.5%), 19 had stable disease (47.5%), and 11 had disease progression (27.5%) (Table 4). All four patients with borderline resectable disease receiving FOLFIRINOX were able to undergo resection afterwards. From the 19 patients with locally advanced disease, 4 (21.1%) were also able to undergo resection after receiving radiation following FOLFIRINOX therapy. From the 18 patients with non-metastatic disease who had imaging available, 9 (50.0%) had stable disease, 5 (27.8%) partial response and 1 (5.6%) had a complete response post treatment with FOLFIRINOX. From the 22 patients with metastatic disease, 14 (63.5%) had either partial response or stable disease.

Table 4. Best response observed in 40 patients with pancreatic adenocarcinoma with imaging available after at least three cycles of FOLFIRINOX. Results are stratified according to the presence of metastatic disease.

	Metastatic disease (n=22)	Non-metastatic disease (n=18)
Complete response	0	1 (5.6%)
Partial response	4 (18.2%)	5 (27.8%)
Stable disease	10 (45.5%)	9 (50.0%)
Progressive disease	8 (36.4%)	3 (16.7%)

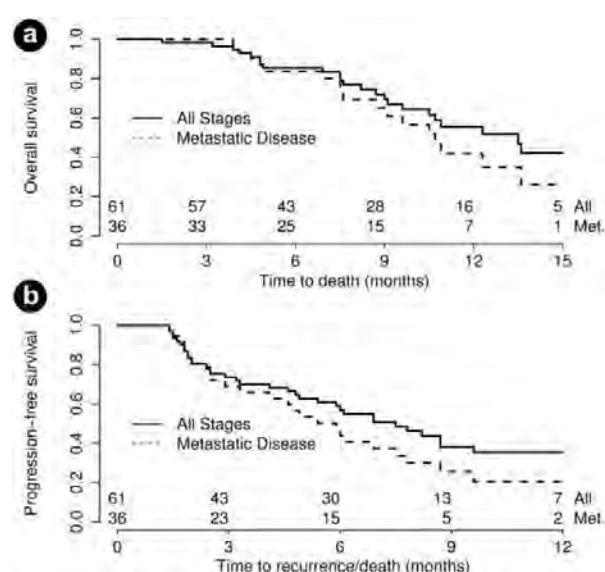
A total of 23 patients died (37.7%) and 29 patients progressed (47.5%). Median progression-free survival was 7.5 months, with 1-year progression-free survival of 35.3%. Overall survival was recorded using medical records and Social Security Death index for all patients. Median overall survival was 13.5 months, with 1-year overall survival of 55.6% (Figure 1). One-year overall survival for patients with metastatic disease was 41.8% compared with 75.5% without metastasis.

DISCUSSION

This is the first study to our knowledge examining FOLFIRINOX use outside of a clinical trial after the ACCORD study in U.S. patients with pancreatic adenocarcinoma [10]. FOLFIRINOX was found to be widely adopted at the centers examined in this study, not only in patients with metastatic disease who were the patient population studied in the ACCORD trial, but also in locally advanced and borderline-resectable disease.

Given concerns for toxicities, FOLFIRINOX dosage was frequently adjusted empirically as well as in response to adverse events. In fact half of the patients were given reduced dosing of FOLFIRINOX starting with the first cycle before the development of any adverse events. Nonetheless, a significant portion of the patients (34.4%) were hospitalized due to adverse events. The rate of hospitalizations was not reported in the ACCORD trial. Only one case of cholangitis was seen, which is reassuring given the high propensity of stents in this patient population. A higher proportion of patients received G-CSF compared to the ACCORD trial (77.0% vs. 42.5%). Accordingly, rates of grade 3-4 neutropenia were lower in our patient population (19.7% vs. 45.7%) but rates of neutropenic fever were similar in both studies at less than 5%.

In spite of dose reductions, FOLFIRINOX was found to be very effective. Rates of response were similar to

**Figure 1.** a. Overall survival in all patients and subset with metastatic disease. b. Progression-free survival for the same patients. (The number of cases exposed to risk are also reported).

the ACCORD study with more than 70% of patients having at least stable disease on therapy. Similar response rates were seen in non-metastatic patients who were not included in the ACCORD trial. In fact, 8 patients were able to undergo resection after FOLFIRINOX therapy. This is notable given the extensive desmoplastic stroma reaction in localized disease and concern for reduced efficacy of chemotherapy in this setting. Progression-free and overall survivals were longer than the results published in the ACCORD trial (7.5 months and 13.5 months, respectively) likely reflecting inclusion of patients with non-metastatic disease. One-year survival rate for patients with metastatic disease was 41.8%, similar to the 48.4% reported in the ACCORD trial.

The strength of this study is that it provides real world data on the use of FOLFIRINOX in patients with pancreatic cancer. Moreover, it provides the first data on patients treated in the U.S.. In addition, it includes patients with non-metastatic disease that were not included in the original ACCORD trial. The use of FOLFIRINOX in these patients has been reported in at least one other retrospective study and is promising [11]. One weakness of this study is that dose reductions were not protocol driven and instead were up to the discretion of the treating oncologists. As a result, it is difficult to judge if all treatment modifications were performed in a standard fashion or were clinically necessary. Similarly, not all physicians obtained tumor markers at regular intervals and therefore our study did not attempt to correlate tumor marker levels with response. Another weakness of this study is that the median age of patients at 58, while similar to the ACCORD study, was much younger than median age of 71 observed in the SEER database [12]. It is therefore important to note that it is not known whether older patients would tolerate this regimen. In regards to the use of G-CSF, rates of febrile neutropenia seen in this study do not justify use of growth factors per NCCN guidelines. However, given that 77.0% of patients received growth factor support, it could be argued that the rates of febrile neutropenia were low only as a result. It may therefore be reasonable to include G-CSF support with this regimen and later discontinue it if not needed.

In conclusion, we believe it is acceptable to use FOLFIRINOX instead of gemcitabine monotherapy in future clinical trials as the new gold standard in patients with pancreatic cancer given its efficacy and acceptable rate of adverse events. It remains to be seen how FOLFIRINOX compares to other regimens currently in clinical trials, such as combination of gemcitabine with nab-paclitaxel, which has had promising results in phase I/II trials [13]. It is also not known whether FOLFIRINOX can serve as a backbone chemotherapy to which targeted agents, such as erlotinib, could be added similarly to what had been done with gemcitabine. Increased toxicity may preclude addition of other agents to FOLFIRINOX.

Use of UTG1A1 testing and appropriate irinotecan dose reduction may be useful in reducing at least some of the toxicities. At the present time, however, FOLFIRINOX by itself is more effective than any other regimen in patients with pancreatic cancer and its toxicities did not preclude its use in the patients studied in this review.

Conflict of interest The author has no potential conflict of interest

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA: A Cancer Journal for Clinicians. 2012; 62(1):10-29.
2. Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 1997; 15(6):2403-13.
3. Di Marco M, Di Cicilia R, Macchini M, et al. Metastatic pancreatic cancer: is gemcitabine still the best standard treatment? (Review). Oncol Rep 2010; 23(5):1183-92.
4. Philip PA, Benedetti J, Corless CL, et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. J Clin Oncol 2010; 28(22):3605-10.
5. Kindler HL, Niedzwiecki D, Hollis D, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). J Clin Oncol 2010; 28(22):3617-22.
6. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007; 25(15):1960-6.
7. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011; 364(19):1817-25.
8. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol 2007; 25(13):1670-6.
9. DCTD, NCI, NIH, DHHS. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0. 2006. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf
10. Assaf E, Verlinde-Carvalho M, Delbaldo C, et al. 5-fluorouracil/leucovorin combined with irinotecan and oxaliplatin (FOLFIRINOX) as second-line chemotherapy in patients with metastatic pancreatic adenocarcinoma. Oncology 2011; 80(5-6):301-6.
11. Hosein PJ, Macintyre J, Kawamura C, et al. A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. BMC Cancer 2012; 12(1):199.
12. Howlader N, Noone A, Krapcho M, Neyman N, Aminou R. SEER Cancer Statistics Review 1975-2009 (Vintage 2009 Populations). Available at: http://seer.cancer.gov/csr/1975_2009_pops09/index.html. Accessed May 10, 2012.
13. Von Hoff DD, Ramanathan RK, Borad MJ, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. J Clin Oncol 2011; 29(34):4548-54.

Appendix RAMANATHAN01

Phase IB/II Randomized Study of FOLFIRINOX Plus Pegylated Recombinant Human Hyaluronidase Versus FOLFIRINOX Alone in Patients With Metastatic Pancreatic Adenocarcinoma: SWOG S1313

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PURPOSE Pegylated recombinant human hyaluronidase (PEGPH20) degrades hyaluronan (HA) and, in combination with chemotherapy, prolongs survival in preclinical models. The activity of PEGPH20 with modified fluorouracil, leucovorin, irinotecan, and oxaliplatin (mFOLFIRINOX) was evaluated in patients with metastatic pancreatic cancer (mPC).

MATERIALS AND METHODS Patients had untreated mPC, a performance status of 0 to 1, and adequate organ function. Tumor HA status was not required for eligibility. After a phase Ib dose-finding study of mFOLFIRINOX plus PEGPH20, the phase II open-label study randomly assigned patients (1:1) to the combination arm or to mFOLFIRINOX alone (n = 138). The primary end point was overall survival (OS).

RESULTS PEGPH20 dosages of 3 μg/kg every 2 weeks were more tolerable than twice-weekly dosages used in the phase I study, so 3 μg/kg every 2 weeks was the phase II dosage. An amendment instituted enoxaparin prophylaxis in the PEGPH20 combination arm as a result of increased thromboembolic (TE) events. The planned interim futility analysis when 35 deaths (of 103 analyzable patients) occurred resulted in an OS hazard ratio (HR) of 2.07 that favored the control arm, and the study was closed to accrual. The treatment-related grade 3 to 4 toxicity was significantly increased in the PEGPH20 combination arm relative to control (odds ratio, 2.7; 95% CI, 1.1 to 7.1). The median OS in the mFOLFIRINOX arm was 14.4 months (95% CI, 10.1 to 15.7 months) versus 7.7 months (95% CI, 4.6 to 9.3 months) in the PEGPH20 combination arm.

CONCLUSION Addition of PEGPH20 to mFOLFIRINOX seems to be detrimental in patients unselected for tumor HA status. This combination caused increased toxicity (mostly GI and TE events) and resulted in decreased treatment duration compared with mFOLFIRINOX alone. The median OS in the mFOLFIRINOX control arm (14.4 months) is, to our knowledge, the longest yet reported and can be considered for patients with good PS.

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INTRODUCTION

The regimens of fluorouracil (FU), leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) and of gemcitabine plus nab-paclitaxel (GA) are the optimal choices for patients with metastatic pancreatic cancer (mPC) who have a good performance status (PS). FOLFIRINOX and GA have a median overall survival (OS) of 11.4 and 8.5 months, respectively, compared with 5.9 to 6.4 months with gemcitabine alone.¹⁻³ Despite these recent advances, the outcome remains poor, and fewer than 10% of patients survive 2 years.^{2,3} A number of new agents are in active investigation, and the tumor stroma has emerged as a key focus of

research in pancreatic cancer.⁴⁻⁷ Primary and metastatic lesions are characterized by a dense desmoplastic stroma in which cancer cells are sparsely scattered.⁸ Hyaluronic acid (hyaluronan, or HA) is a major component of this extracellular matrix. Preclinical studies have shown that high levels of HA in the extracellular matrix promote tumorigenesis.⁷⁻⁹ Unmodified hyaluronidase has been used clinically, but a short half-life limits cancer applications. The pegylated form of human recombinant hyaluronidase (PEGPH20) has superior pharmacologic characteristics and, in preclinical models, depletes HA in the cancer extracellular matrix.^{9,10} A phase I study of

ASSOCIATED CONTENT

See accompanying Editorial on page 1041 Appendix Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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Clinical trial information: NCT01959139.

PEGPH20 in solid tumors established the tolerable dosage as 3 µg/kg given intravenously (IV) twice per week. In patients with pre- and post-dose tumor biopsies (n = 6), a decrease in tumor HA levels was observed, and Dynamic Contrast Enhanced magnetic resonance imaging (n = 11) showed changes in tumor perfusion consistent with the postulated mechanism of action.¹¹ Studies in genetically engineered mouse models of pancreatic cancer sparked interest in evaluation of PEGPH20 in clinical trials for mPC.^{12,13} Rapid depletion of tumor HA after PEGPH20 administration was seen and resulted in significantly improved survival for the combination of gemcitabine and PEGPH20 compared with gemcitabine alone.^{12,13} Subsequently, a phase Ib study evaluated gemcitabine and PEGPH20 in patients with mPC (n = 28). The phase II dosage was gemcitabine 1,000 mg/m² per week with the PEGPH20 dosage of 3.0 µg/kg twice per week for 4 weeks then once per week for 3 weeks. The median progression-free survival (PFS) was 5.0 months, and the median OS was 6.6 months. High HA levels were seen in 35% of 17 tumor samples analyzed using a validated immunohistochemical assay. The response rate (RR) of 67%, the PFS (7.2 months), and the OS (13.0 months) favored the subset of patients with high HA levels (n = 6).¹⁴ Subsequently, a randomized phase II study of combined PEGPH20 and GA was initiated ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT01839487 [Halo-109-202]). In parallel, the Southwest Oncology Group initiated a randomized, phase Ib/II study of PEGPH20 and FOLFIRINOX ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT01959139 [S1313]). Neither study selected patients according to HA tumor status.

MATERIALS AND METHODS

Eligibility Criteria

Pertinent eligibility criteria are as follows: age 18 to 75 years, Zubrod PS of 0 to 1, and measurable mPC. Adequate organ function was required (normal serum creatinine and bilirubin level). A pretreatment tumor sample was required for registration. Exclusion criteria included the following: prior therapy for mPC, exposure to oxaliplatin or irinotecan at least 3 years before registration, prior abdominal radiation, receipt of warfarin or megestrol acetate, and history of pre-existing carotid artery disease or arterial thromboembolic (TE) events that required intervention or treatment.

Treatments

Each 2-week cycle of mFOLFIRINOX consisted of oxaliplatin 85 mg/m², leucovorin 400 mg/m², irinotecan 180 mg/m², and FU 2,400 mg/m² (by 46-h IV infusion) given according to published guidelines.³ The FU bolus was omitted (the FOLFIRINOX modification). All patients received pegfilgrastim or filgrastim after disconnection of the FU ambulatory pump. PEGPH20 was provided by Halozyme Pharmaceuticals (San Diego, CA). PEGPH20 was administered IV over 10 minutes, 24 hours before each

dose of mFOLFIRINOX. The administration of PEGPH20 required corticosteroid premedication before and after dosing (ie, dexamethasone 8 mg twice per day by mouth or IV on day 1 of dosing, then 4 mg twice per day for the 3 subsequent days) to reduce the incidence of myalgias and arthralgias. The protocol was subsequently amended to require the use of prophylactic enoxaparin 1 mg/kg per day beginning 1 day before treatment with PEGPH20 because of an imbalance in TE events in this and the parallel Halo-109-202 study.

Phase Ib Study Design

The phase I part was a standard 3 plus 3, limited dose de-escalation study to evaluate safety and to determine a recommended phase II dose of PEGPH20. Potential PEGPH20 dose levels in a 2-week cycle included 3 µg/kg on day 1 and day 3 or 4; 3 µg/kg on day 1 only; and 1.6 µg/kg on day 1 only. The study schema and dose-limiting toxicity (DLT) definitions are listed in Appendix [Table A1](#) (online only).

Phase II Study Design

The primary end point of the phase II study was OS in patients treated with PEGPH20 plus mFOLFIRINOX compared with those treated with mFOLFIRINOX alone. We hypothesized a hazard ratio (HR) of 0.67 in a comparison of the two arms, with the assumption that the investigational arm would improve median survival from 10 months with mFOLFIRINOX alone to 15 months in combination. With a one-sided type I error of 10% and 80% power, this design required 138 eligible patients. Secondary objectives were to assess the PFS, the RR, and the toxicity profile. Translational objectives were to correlate cancer antigen 19-9 (CA 19-9) levels, plasma HA levels, and tumor HA levels with clinical outcomes of treated patients. The study did not require stratification or selection on the basis of tumor HA status.

Patients were seen every 2 weeks for a history and physical examination with routine blood tests. The CA19-9 level was measured at baseline and every 4 weeks. Dose reductions for mFOLFIRINOX followed published guidelines.³ The PEGPH20 dose could be reduced to 1.6 µg/kg on day 1 if specific drug-related grade 3 or 4 toxicity occurred (eg, musculoskeletal toxicity). Patients were removed from the study if an arterial TE event or a grade 4 venous TE event occurred during the study or if a patient was receiving enoxaparin at the start of study. Adverse events (AEs) were assessed for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.¹⁵ Patients were evaluated for tumor response every 8 weeks by RECIST, version 1.1, criteria.¹⁶

Tumoral and Serum HA Studies

A total of 10 mL of whole blood was collected at baseline, 48 hours after the first PEGPH20 dose, before cycle 2, and before cycle 3. Serum HA analysis was performed by Micro

Constants (San Diego, CA). Paraffin-embedded tissue or five unstained slides from diagnosis of metastatic tumor were required for tumor HA assay. A Clinical Laboratory Improvement Amendments certified laboratory performed the assays (Ventana Medical Systems, Tucson, AZ), and high HA was defined as extracellular matrix HA tumor staining $\geq 50\%$.

Random Assignment

In the open-label, phase II study, patients were randomly assigned in a 1:1 manner into the two treatment groups. Assignment used a dynamic balancing algorithm¹⁷ with stratification by Zubrod PS (0 v 1).

Statistical Analysis

The primary analysis of OS was conducted in all eligible patients according to a modified intent-to-treat principle. Probabilities of OS and PFS were estimated using the Kaplan-Meier method. Statistical differences in event rates between treatment arms were assessed via stratified Cox regression model. An interim futility analysis of OS was planned when one third of the expected events (approximately 37 deaths) was observed. Evidence to suggest early closure would consist of rejection of the alternative hypothesis (HR of 0.67 for OS) at a one-sided alpha level of .07. RR was compared by treatment arm via χ^2 test in patients with measurable disease. The mean number of treatment cycles per patient was compared across treatment arms using a Wilcoxon rank-sum test. Proportions of patients who experienced grades 3 to 5 toxicities were

compared by treatment arm using an odds ratio estimated by simple logistic regression. Statistical tests were reported as two sided.

RESULTS

This was a study conducted by the Southwest Oncology Group (SWOG) and National Clinical Trials Network. Participating site institutional review board approval and patient written informed consent were obtained before trial enrollment.

Phase I

The study opened to accrual in January 2014 at limited SWOG institutions. At dose-level 1 (PEGPH20 3 $\mu\text{g/kg}$ on day 1 and day 3 or 4 of each cycle), two DLTs (myalgia and fatigue/mucositis) were observed in the first five patients enrolled. This cohort was closed because of intolerability and dose-level 2 (PEGPH20 at 3 $\mu\text{g/kg}$ on day 1 only, every 2 weeks) accrued six patients. One patient experienced DLTs (AST/ALT elevation, fatigue, dehydration, sepsis), and the phase II dosage was established as PEGPH20 at 3 $\mu\text{g/kg}$ on day 1 with mFOLFIRINOX on days 2 to 4 every 2 weeks.

Study Amendments

The study temporarily closed to accrual in April 2014 after two patients were enrolled in the phase I part, when the parallel Halo-109-202 study was suspended because of the higher-than-expected TE rate in the PEGPH20-and-GA

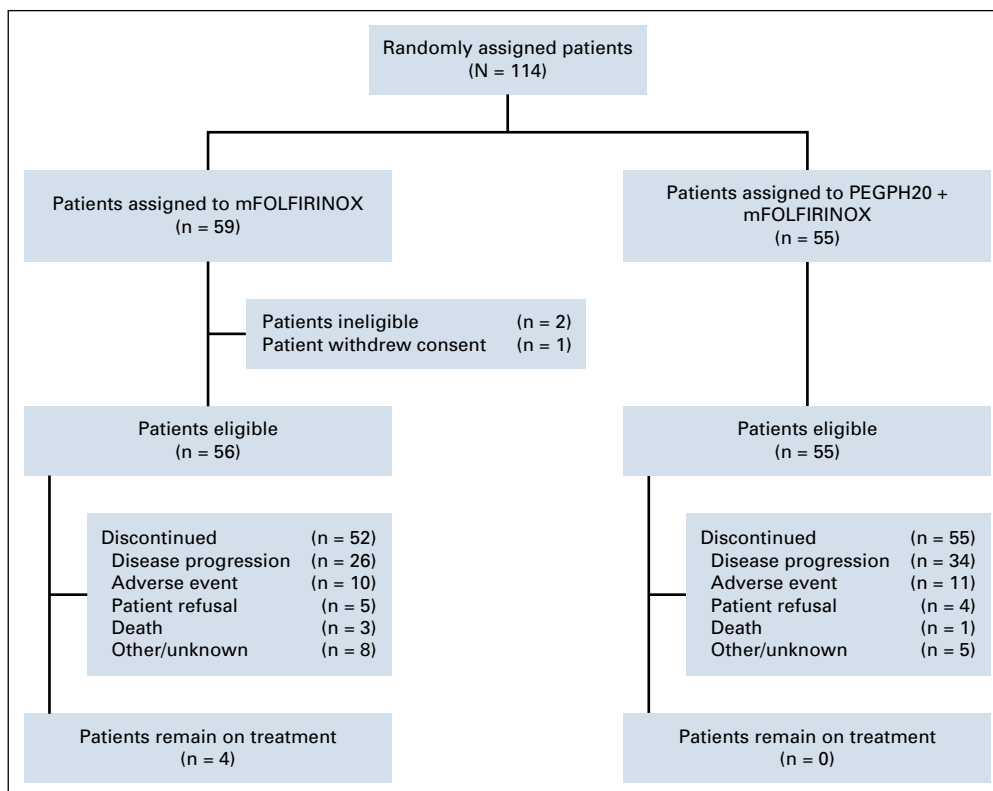


FIG 1. CONSORT flow diagram. mFOLFIRINOX, modified fluorouracil, leucovorin, irinotecan, and oxaliplatin; PEGPH20, pegylated recombinant human hyaluronidase.

arm. To reduce the risk of TE events, a study amendment (October 2014) required patients to receive aspirin 81 mg/d, and those with a history of TE events or who received warfarin were excluded. After the phase II study was activated in May 2015, a preplanned interim safety analysis after 40 patients were randomly assigned and completed two cycles was performed in March 2016. Imbalance in all-grade TE events was noted in the PEGPH20-plus-mFOLFIRINOX arm compared with the control arm (38% v 11%). There were no arterial TE events. Aspirin was replaced by enoxaparin prophylaxis (1mg/kg subcutaneously per day or equivalent) for the PEGPH20-plus-mFOLFIRINOX arm only. Ongoing toxicity analysis revealed higher-than-expected levels of nausea, vomiting, and diarrhea in the PEGPH20-plus-mFOLFIRINOX arm. An amendment (October 2016) recommended that patients on the mFOLFIRINOX-plus-PEGPH20 arm receive antiemetics suitable for a highly emetogenic regimen, prophylactic use of loperamide per guidelines for the first sign of diarrhea, and a lower threshold grade 2 or greater diarrhea for dose reduction and delay of chemotherapy. On March 14, 2017, accrual was suspended on the basis of the results of a planned interim futility analysis; the study was permanently closed in July 2017.

Patient Characteristics

The randomized, phase II study accrued 114 patients from May 2015 to March 2017 at 30 SWOG member institutions. Three patients were excluded from the efficacy analysis: two patients were ineligible, and one withdrew consent (Fig 1). Patient characteristics (n = 111) are listed in Table 1.

Safety and Toxicity

The safety analysis included 105 patients, because six did not receive protocol therapy. In the mFOLFIRINOX arm (n = 54), there was one death as a result of sepsis. Four patients had grade 4 treatment-related AEs: neutropenia, hypokalemia, decreased platelets, and sepsis. An additional 26 patients had grade 3 toxicities (Table 2). Of the 51 patients assessed for AEs on the PEGPH20-plus-mFOLFIRINOX arm, seven patients had grade 4 treatment-related AEs, including hypokalemia, hyperglycemia, infusion-related reaction, decreased lymphocytes, sepsis, TE, and vomiting. Thirty-three additional patients experienced grade 3 AEs, including four TE events and one GI bleed (Table 2). The incidence of TE events in the PEGPH20 arm decreased from 33% to 9% after enoxaparin prophylaxis. The treatment exposure was higher in the mFOLFIRINOX arm compared with the combined arm (Appendix Table A2, online only). Dose delays and severe AEs were all increased in the PEGPH20-plus-mFOLFIRINOX arm compared with the mFOLFIRINOX arm (Table 2).

Efficacy

OS was statistically significantly longer in the mFOLFIRINOX arm (n = 56, and 30 deaths) compared with the PEGPH20-plus-mFOLFIRINOX arm (n = 55, and 40

TABLE 1. Patient Characteristics

Characteristic	% of Patients	
	mFOLFIRINOX (n = 56)	mFOLFIRINOX Plus PEGPH20 (n = 55)
Age, years		
Median	61	64
Range	32-75	40-74
Sex		
Male	55	44
Female	45	56
Ethnicity		
White	82	78
Black	7	2
Asian	7	13
Other	4	7
Zubrod PS		
0	55	58
1	45	42
Primary site		
Head of pancreas	29	35
Body of pancreas	29	29
Tail of pancreas	27	20
Pancreas, NOS	16	17
Sites of involvement		
Primary tumor/ pancreas	91	89
Regional lymph nodes	39	29
Distant lymph nodes	11	9
Lung	32	25
Liver	80	76
Peritoneum	21	20
Other	21	16
Serum CA 19-9, U/mL		
< 37	18	13
≥ 37	82*	87†
Prior treatment (for PC)		
Chemotherapy	5	7
Surgery	4	13

Abbreviations: CA 19-9, cancer antigen 19-9; mFOLFIRINOX, modified fluorouracil, leucovorin, irinotecan, and oxaliplatin; NOS, not otherwise specified; PC, pancreatic cancer; PEGPH20, pegylated recombinant human hyaluronidase; PS, performance status.

*No. of patients = 46; median, 4,840; range, 91 to 232,548.

†No. of patients = 48; median, 3,465; range, 52 to 416,315.

deaths). The median OS durations were 14.4 versus 7.7 months, respectively (HR, 2.07; 95% CI, 1.28 to 3.34; $P < .01$; Fig 2). Similarly, the median PFS was longer in the

TABLE 2. Treatment-Related Toxicities That Occurred in More Than 10% of Patients and Those of Special Interest in the Phase II Study

Toxicity	No. (%) of Patients			
	mFOLFIRINOX (n = 54)		mFOLFIRINOX Plus PEGPH20 (n = 51)	
	Grade 1 and 2	Grade 3 and 4	Grade 1 and 2	Grade 3 and 4
Elevated ALT	15 (28)	0	9 (18)	3 (6)
Elevated AST	14 (26)	0	11 (22)	0
Abdominal pain	10 (19)	1 (2)	10 (20)	3 (6)
Elevated alkaline phosphatase	14 (26)	0	13 (25)	2 (4)
Alopecia	12 (22)	0	10 (20)	0
Anemia	31 (57)	4 (7)	30 (59)	2 (4)
Anorexia	19 (35)	2 (4)	21 (41)	3 (6)
Arthralgia	4 (7)	0	5 (10)	1 (2)
Constipation	11 (20)	0	11 (22)	0
Diarrhea	29 (54)	10 (19)	26 (51)	12 (24)
Dysgeusia	11 (20)	0	13 (25)	0
Edema in limbs	7 (13)	0	8 (16)	3 (6)
Fatigue	34 (63)	6 (11)	28 (55)	10 (20)
Febrile neutropenia/sepsis	0	2* (4)	0	1 (2)
Muscle weakness	1 (2)	0	1 (2)	0
Hypoalbuminemia	16 (30)	0	14 (27)	0
Hyponatremia	7 (13)	1 (2)	6 (12)	3 (6)
Infusion reaction	6 (11)	0 (6)	6 (12)	1 (2)
Mucositis	10 (19)	0	6 (12)	4 (8)
Myalgias	4 (7)	0	17 (33)	2 (4)
Nausea	24 (44)	8 (15)	27 (53)	13 (25)
Paresthesias	9 (17)	1 (2)	7 (14)	0
Peripheral neuropathy (motor)	1 (2)	1 (2)	4 (8)	1 (2)
Peripheral neuropathy (sensory)	30 (56)	2 (4)	18 (35)	6 (12)
Platelets	25 (46)	2 (4)	15 (29)	3 (6)
Thromboembolic events	1 (2)	1 (2)	4 (8)	5 (10)
Vomiting	18 (33)	7 (13)	13 (25)	11 (22)
Weight loss	14 (26)	1 (2)	23 (45)	0
White count	7 (13)	2 (4)	7 (14)	1 (2)
Maximum grade, any event	20 (37)	31 (57)	8 (16)	40 (78)
SAE (all grades, regardless of treatment attribution)	8 (15)		36 (71)	
SAE grade $\geq$ 3 (regardless of treatment attribution)	6 (11)		34 (67)	
Treatment-related SAE (all grades)	5 (9)		23 (45)	

NOTE. All grades 3 to 5 toxicities were increased in the PEGPH20-plus-mFOLFIRINOX arm (odds ratio, 2.7; 95% CI, 1.1 to 7.1).

Abbreviations: mFOLFIRINOX, modified fluorouracil, leucovorin, irinotecan, and oxaliplatin; PEGPH20, pegylated recombinant human hyaluronidase; SAE, serious adverse event.

*There was one death as a result of sepsis that occurred during the study in the mFOLFIRINOX arm.

control (n = 41 events) versus experimental arm (n = 48 events): 6.2 versus 4.3 months, respectively (HR, 1.74; 95% CI, 1.14 to 2.66; $P = .01$; Fig 3). The control arm of mFOLFIRINOX had a higher RR of 45% (95% CI, 32% to 58%) than the PEGPH20-plus-mFOLFIRINOX arm RR of

33% (which included two complete responses; 95% CI, 20% to 45%), although this difference did not reach statistical significance ($P = .20$; Table 3). In the mFOLFIRINOX arm, 73% received second-line therapy: 62% received GA, and a smaller number (11%) continued with a modification

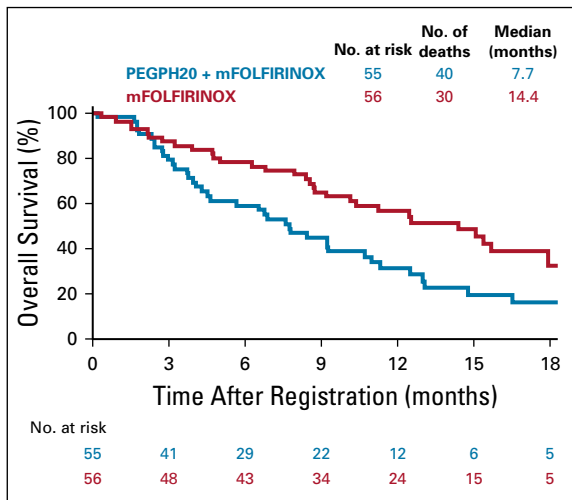


FIG 2. Overall survival. mFOLFIRINOX, modified fluorouracil, leucovorin, irinotecan, and oxaliplatin; PEGPH20, pegylated recombinant human hyaluronidase.

of FOLFIRINOX. In the PEGPH20-plus-mFOLFIRINOX arm, 58% received second-line therapy: 47% received GA, and 11% continued with a modification of FOLFIRINOX.

CA 19-9 levels. The CA 19-9 levels were checked at baseline and every 4 weeks. The maximum percentage decrease in CA 19-9 from baseline was defined as high ($\geq 50\%$ decrease) versus low ($< 50\%$ decrease). Of the 20 patients on the PEGPH20-plus-mFOLFIRINOX arm with follow-up data, nine (45%) had a 50% or greater decrease in CA 19-9 that was associated with improved RR ($P = .04$) and PFS ($P = .04$) but not OS ($P = .27$). Of the 32 patients on the mFOLFIRINOX arm with follow-up data, 17 (53%) had a 50% or greater decrease in CA 19-9 that was

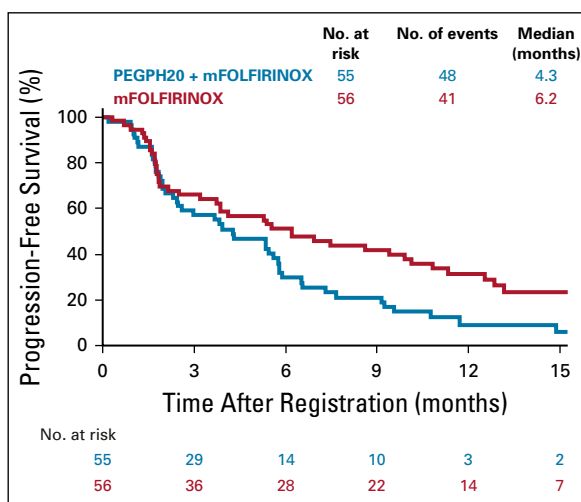


FIG 3. Progression-free survival. mFOLFIRINOX, modified fluorouracil, leucovorin, irinotecan, and oxaliplatin; PEGPH20, pegylated recombinant human hyaluronidase.

associated with improved RR ($P = .04$), PFS ($P = .01$), and OS ($P = .07$).

Tumoral and Plasma HA

Plasma HA. Samples were assayed for total HA concentration using a validated method that measures pharmacodynamic response to PEGPH20 (MicroConstants, San Diego, CA) in the PEGPH20 + mFOLFIRINOX arm only. Baseline circulating HA levels ranged from 29-838 ng/mL ($n = 49$, median 99). Consistent with previously published results (11), HA levels increased by a median of 33,708 ng/mL ($n = 42$, range 49-290,896 ng/mL), or over 300-fold at the 48-hour blood draw, demonstrating PEGPH20 activity.

Tumor HA. Tumor HA analysis and scoring was done with a validated immunohistochemistry test (Ventana Medical Systems, Tucson, AZ), as used in the Halo-109-202 study. This test was Clinical Laboratory Improvement Amendments certified for slides fewer than 90 days old; only 11 specimens in the SWOG biospecimen bank met these requirements, and eight were evaluable (results not shown).

DISCUSSION

The inferior outcomes in all efficacy measures (OS, PFS, and RR) with the addition of PEGPH20 to mFOLFIRINOX was unexpected, and the negative effect on survival (median OS of 7.7 months for the combination arm compared with 14.4 months for the mFOLFIRINOX-alone arm) is striking. The observed rate of expected AEs for the control arm of mFOLFIRINOX, such as nausea, diarrhea, neuropathy, fatigue, and neutropenic fever, was remarkably low compared with published data and was partly explained by the mFOLFIRINOX regimen and growth factor support.³ In contrast, the addition of PEGPH20 to mFOLFIRINOX significantly increased GI toxicity and TE events. Enoxaparin prophylaxis was required to reduce TE events comparable to control arm occurrences. Because of toxicity, patients in the combination arm had increased dose delays, dose reductions, and reduced drug exposure of FOLFIRINOX. It is likely that lower overall drug exposure in patients who received the combination (median, four cycles *v* eight for mFOLFIRINOX alone) contributed to inferior survival. Another hypothesis is that PEGPH20 combined with the mFOLFIRINOX backbone had an unexpected negative effect on the tumor microenvironment or an adverse drug interaction with one or more of the FOLFIRINOX components, such as granulocyte colony-stimulating growth factor. Despite the incomplete tumor HA analysis because a majority of slides were more than 90 days old, it is unlikely, but not definitive that the median OS of patients with high-HA tumors (percentage not determined) treated in the combination arm would equal or exceed the 14.4 months seen in the mFOLFIRINOX-alone arm.

In contrast to this study (ie, S1313), the recently published, randomized Halo-109-202 study shows promise with the

TABLE 3. Response Rate

Type	Response (%)	
	mFOLFIRINOX (n = 56)	mFOLFIRINOX Plus PEGPH20 (n = 55)
Complete response	0	4
Partial response	45	29
Stable disease	20	24
Response rate	45 (95% CI, 32 to 58)	33 (95% CI, 20 to 45)

Abbreviations: mFOLFIRINOX, modified fluorouracil, leucovorin, irinotecan, and oxaliplatin; PEGPH20, pegylated recombinant human hyaluronidase.

addition of PEGPH20 to GA.¹⁸ Similar to the S1313 study, TE events increased with the addition of PEGPH20, and patients required enoxaparin. In our study, we also determined that enoxaparin was necessary, because low-dose aspirin (in the first 40 randomly assigned patients) did not completely eliminate TEs. The AE profile of the PEGPH20-plus-GA arm was acceptable. The tumor high-HA rate was 34%. In this subset of high-HA tumors, efficacy parameters favored the addition of PEGPH20; the RR was 45% versus 31%, the median PFS was 9.2 versus 5.2 months (HR, 0.51; 95% CI, 0.26 to 1.00; $P = .048$), and the median OS was 11.5 versus 8.5 months (HR, 0.96; 95% CI, 0.57 to 1.61). There are several important differences between S1313 and Halo-109-202. PEGPH20 (3 ug/kg) could be administered on a twice-a-week schedule with weekly GA (days 1, 8, and 15); thus, patients received six doses in the first 4 weeks compared with only three doses of mFOLFIRINOX (days 1, 14 and 28). In the phase IB part of S1313, twice-a-week administration of PEGPH20 (six doses in the first 4 weeks) with mFOLFIRINOX was toxic and caused enhanced fatigue and general intolerance, so it required reduction in the frequency of dosing. Other differences between Halo-109-202 and S1313 are accrual (279 v 114), end points (PFS v OS), HA

tumor analysis (246 v 11), and interim analysis (no v yes). Halo-109-301 is a multinational, double-blind, phase III, randomized study to evaluate PEGPH20 with GA in high-HA tumors only ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02715804) identifier: NCT02715804). The study is ongoing at this time and is without any safety issues reported by the sponsor.

The control arm of mFOLFIRINOX was remarkably well tolerated and resulted in a median OS of 14.4 months, which is—to our knowledge—the highest reported for this regimen. Because of concerns of toxicity, many oncologists reduce the dose of one or more of the components (FU, oxaliplatin, or irinotecan) by 15% to 25%.¹⁹⁻²² We chose to modify the regimen by omitting bolus FU (which is a common modification of the FOLFOX regimen) without any other modifications, and we opted to give prophylactic growth factor support. On the basis of the results of S1313, mFOLFIRINOX can be considered for patients with good PS. The use of prophylactic granulocyte growth factor support with cycle 1 may not be needed in all cases and can be given per institutional guidelines.²³ TE events should be identified early and appropriately treated. There was one death as a result of sepsis in the mFOLFIRINOX arm, so oncologists are cautioned about the need for careful selection and monitoring of patients with mPC during therapy.

Stromal targeting agents should be evaluated cautiously given the negative results of Hedgehog inhibitors (vismodegib and saredigib) when combined with gemcitabine in phase II, randomized studies.^{24,25} In summary, the results of S1313 highlight the importance of preclinical research when multiple agents are evaluated as well as the importance of robust clinical trial design and conduct with appropriate safety reviews. With close monitoring of toxicities as they emerged and appropriate study interim analyses, we stopped the study early for inferior survival in the investigational arm. We expect that other ongoing clinical and preclinical studies will give additional insights.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES

- Sohal DP, Mangu PB, Khorana AA, et al: Metastatic pancreatic cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 34:2784-2796, 2016
- Von Hoff DD, Ervin T, Arena FP, et al: Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 369:1691-1703, 2013
- Conroy T, Desseigne F, Ychou M, et al: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 364:1817-1825, 2011
- Krantz BA, O'Reilly EM: Biomarker-based therapy in pancreatic ductal adenocarcinoma: An emerging reality? *Clin Cancer Res* 24:2241-2250, 2018
- Tesfaye AA, Kamgar M, Azmi A, et al: The evolution into personalized therapies in pancreatic ductal adenocarcinoma: Challenges and opportunities. *Expert Rev Anticancer Ther* 18:131-148, 2018
- Ahn DH, Ramanathan RK: Targeting the stroma in pancreatic cancer. *Linchuang Zhongliuxue Zazhi* 6:65, 2017
- Vennin C, Murphy KJ, Morton JP, et al: Reshaping the tumor stroma for treatment of pancreatic cancer. *Gastroenterology* 154:820-838, 2018
- Whatcott CJ, Diep CH, Jiang P, et al: Desmoplasia in Primary tumors and metastatic lesions of pancreatic cancer. *Clin Cancer Res* 21:3561-3568, 2015
- Wong KM, Horton KJ, Coveler AL, et al: Targeting the tumor stroma: The biology and clinical development of pegylated recombinant human hyaluronidase (PEGPH20). *Curr Oncol Rep* 19:47, 2017
- Thompson CB, Shepard HM, O'Connor PM, et al: Enzymatic depletion of tumor hyaluronan induces antitumor responses in preclinical animal models. *Mol Cancer Ther* 9:3052-3064, 2010
- Infante JR, Korn RL, Rosen LS, et al: Phase 1 trials of PEGylated recombinant human hyaluronidase PH20 in patients with advanced solid tumours. *Br J Cancer* 118:153-161, 2018
- Jacobetz MA, Chan DS, Neesse A, et al: Hyaluronan impairs vascular function and drug delivery in a mouse model of pancreatic cancer. *Gut* 62:112-120, 2013
- Provenzano PP, Cuevas C, Chang AE, et al: Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. *Cancer Cell* 21:418-429, 2012
- Hingorani SR, Harris WP, Beck JT, et al: Phase Ib study of PEGylated recombinant human hyaluronidase and gemcitabine in patients with advanced pancreatic cancer. *Clin Cancer Res* 22:2848-2854, 2016
- National Cancer Institute: Cancer Therapy Evaluation Program: Common Terminology Criteria for Adverse Events. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
- Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 45:228-247, 2009
- Pocock SJ, Simon R: Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 31:103-115, 1975
- Hingorani SR, Zheng L, Bullock AJ, et al: HALO 202: Randomized phase II study of PEGPH20 plus nab-paclitaxel/gemcitabine versus nab-paclitaxel/gemcitabine in patients with untreated, metastatic pancreatic ductal adenocarcinoma. *J Clin Oncol* 36:359-366, 2018
- Usón JrPLSJr, Rother ET, Maluf FC, et al: Meta-analysis of modified FOLFIRINOX regimens for patients with metastatic pancreatic cancer. *Clin Colorectal Cancer* 17:187-197, 2018
- Ozaka M, Ishii H, Sato T, et al: A phase II study of modified FOLFIRINOX for chemotherapy-naïve patients with metastatic pancreatic cancer. *Cancer Chemother Pharmacol* 81:1017-1023, 2018
- Chlamma MK, Cook N, Dhani NC, et al: FOLFIRINOX for advanced pancreatic cancer: The Princess Margaret Cancer Centre experience. *Br J Cancer* 115:649-654, 2016
- Mahaseeth H, Brutchter E, Kauh J, et al: Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. *Pancreas* 42:1311-1315, 2013
- Smith TJ, Bohlke K, Lyman GH, et al: Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 33:3199-3212, 2015
- Catenacci DV, Junttila MR, Karrison T, et al: Randomized phase Ib/II study of gemcitabine plus placebo or vismodegib, a Hedgehog pathway inhibitor, in patients with metastatic pancreatic cancer. *J Clin Oncol* 33:4284-4292, 2015
- The Olive Laboratory: Clinical trial: IPI-926-03. <https://www.olivelab.org/ipi-926-03.html>



AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Phase IB/II Randomized Study of FOLFIRINOX Plus Pegylated Recombinant Human Hyaluronidase Versus FOLFIRINOX Alone in Patients With Metastatic Pancreatic Adenocarcinoma: SWOG S1313

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APPENDIX

TABLE A1. Dose-Limiting Toxicity and Study Schema

Dose-limiting toxicity
Drug-related toxicities that occurred in the first cycle (2-week period) of treatment that were attributable to PEGPH20 and/or mFOLFIRINOX (possible, probable, or definite)
Any grade 3 or greater nonhematologic toxicity (except alopecia and grade 3 nausea, vomiting, and diarrhea that responded to medical treatment within 72 hours)
Hematologic toxicities, including grade 4 anemia or thrombocytopenia, grade 4 ANC decrease that lasted more than 7 days, or grade 3 or greater febrile neutropenia
Laboratory test results including grade 3 or greater elevation of AST/ALT, total bilirubin, or creatinine (if baseline values were elevated, then increase should be by two grades to be called a dose-limiting toxicity)
A delay in starting the second cycle of mFOLFIRINOX by more than 2 weeks because of drug-related toxicity.
Study schema
The schema included enrollment of a cohort of six patients treated with mFOLFIRINOX and PEGPH20 starting at dose-level 1 (3 µg/kg on day 1 and on day 3 or 4).
If two or more patients at dose level 1 experienced a dose-limiting toxicity, PEGPH20 was reduced for the next cohort (3 µg/kg on day 1 only).
If dose reduction to dose-level 3, then the study would be modified or closed (PEGPH20 at 1.6 µg/kg on day 1 only).
If none or one patient experienced a dose-limiting toxicity in a cohort of six patients, then that dose level was chosen as the phase II dose.

Abbreviations: ANC, absolute neutrophil count; mFOLFIRINOX, modified fluorouracil, leucovorin, irinotecan, and oxaliplatin; PEGPH20, pegylated recombinant human hyaluronidase.

TABLE A2. Treatment Exposure

Variable	No. (%) of Patients	
	mFOLFIRINOX (n = 56)	mFOLFIRINOX Plus PEGPH20 (n = 55)
Median (range) treatment, cycles	8 (0-37)	4 (0-43)*
Treatment administered, cycles		
≥ 2	47 (84)	45 (82)
≥ 4	42 (75)	34 (62)
≥ 6	33 (59)	23 (42)
≥ 8	29 (52)	21 (38)

Abbreviations: mFOLFIRINOX, modified fluorouracil, leucovorin, irinotecan, and oxaliplatin; PEGPH20, pegylated recombinant human hyaluronidase.

**P* = .05.

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Appendix RATAIN02

Phase II Oncology Trials: Let's Be Positive

Mark J. Ratain

The critical decision in drug development is often at the end of phase II, as phase III trials are an expensive undertaking, with the potential for significant corporate and public consequences in the event of a negative phase III trial. Thus, retrospective analyses of the usefulness of phase II trials are welcomed and valued, as illustrated by the study of Goffin et al. (1). In this analysis of 58 cytotoxic drugs, 46 studied in phase II, the authors show a statistical relationship between objective response rate and probability of approval of the drug, with the important exception of responses in metastatic melanoma and renal cell carcinoma.

Most readers will not be surprised by the authors' findings of a relationship between phase II response rate and subsequent marketing of the drug. A drug may show activity in a specific disease in phase I or II, however, but may not be developed further in that disease because of business concerns. Thus, one would expect a bias towards phase III trials in diseases with larger markets, generally considered to be breast, colorectal, lung, and prostate cancers. Therefore, a lower approval rate in melanoma and renal cell cancer could potentially be affected by a lower number of phase III trials in these indications with smaller markets. In fact, Goffin et al. (1) did not address whether or not phase III trials were conducted with those agents that had phase II response rates of 10% or more. One cannot firmly conclude, therefore, that the phase II results were not predictive for phase III results in melanoma and renal cell cancer, as opposed to an alternative explanation that there was relatively little interest in seeking approval for these indications. What have we learned from this analysis? It is important to emphasize that a correlation, albeit significant, does not necessarily result in usefulness. A more important issue is the usefulness of phase II oncology trials, particularly in the context of predicting marketing approval for the indication studied in the specific phase II trial. To address this question, the data of Goffin et al. (1) have been reanalyzed using standard approaches to studying diagnostic tests. In this context, one normally uses metrics such as sensitivity, specificity, and predictive value (2). To assess this, one can consider various objective response rate cutoffs, as illustrated in Table 1, such as cutoffs of 10% and 20%. Sensitivity, or true positive rate, is defined as the percentage of drugs approved for an indication for which the phase II trial exceeded the threshold response rate. (It should be noted that if no drugs were approved for an

indication, it is not possible to calculate the sensitivity). Specificity, or true negative rate, is defined as the percentage of drugs not approved for an indication for which the phase II trial did not exceed the threshold response rate. Positive predictive value is the likelihood of approval (for a disease) given a positive phase II trial (i.e., exceeding threshold response rate). Negative predictive value is the likelihood of not being approved for a disease (regardless of whether a phase III trial was conducted) given a negative phase II trial (i.e., not exceeding threshold response rate).

When the data of Goffin et al. (1) were reanalyzed in this way (Table 1), it is clear that phase II oncology trials have a high negative predictive value but a low positive predictive value. Sensitivity was high at a threshold response rate of 10%, as this would be expected to exclude few active agents. At a higher threshold response rate of 20%, there was greater specificity but with some tradeoff on sensitivity.

Is response rate the right end point for phase II oncology trials? This paradigm has recently been questioned in the context of the development of noncytotoxic agents (3). The data of Goffin et al. suggest that we should consider rejecting our current paradigm for cytotoxic agents as well, particularly if the goal of phase II studies is to predict for phase III success. Oncology has been recently singled out as a therapeutic area for which positive phase II trials have not been predictive of phase III success (4). As noted in Table 1, the best positive predictive value was for non-small-cell lung cancer, in which 75% of agents whose phase II response rate exceeded 20% were subsequently approved. Unfortunately, this threshold would have excluded two of our currently approved cytotoxic agents for non-small-cell lung cancer as only three of the five approved agents in this study met this criterion.

Moving forward, it is critical to consider the purpose of phase II trials. In essentially all other therapeutic areas, such studies are usually randomized, dose-ranging controlled trials, often including a placebo group, but enable determination of the relationship between dose and an end point of clinical interest, and, by extension, provide evidence of activity (5). Most importantly, phase III trials are expected to confirm findings of phase II studies, and, outside of oncology, are generally positive; consequently, phase II trials in other therapeutic areas have a high positive predictive value (4, 6). In contrast, oncology trials have a high negative predictive value but a relatively low positive predictive value (Table 1). These features may be due to the nature of cancer and anticancer agents. On the other hand, these may be due to the differences in the designs used for phase II trials in oncology, in which the classic designs are formally aimed at proving that the drug does not have activity (7). In fact, a trial that is not negative is not necessarily "positive," as borne out by the low positive predictive value for marketing approval, presumably due in a large part to the low phase III success rate.

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Table 1. Analysis of usefulness of phase II results to predict drug approval within disease category by threshold response rate (using data from Goffin et al.)

	Melanoma (n = 29)	Renal (n = 15)	Breast (n = 26)	NSCLC (n = 25)	Ovarian (n = 22)	Colorectal (n = 28)
ORR > 10%						
SE (%)	?	?	100	80	100	100
SP (%)	84	93	50	70	85	88
PPV (%)	0	0	25	40	33	57
NPV (%)	100	100	100	93	100	100
ORR > 20%						
SE (%)	?	?	100	60	67	50
SP (%)	95	93	77	95	80	96
PPV (%)	0	0	44	75	33	67
NPV (%)	100	100	100	90	80	92

Abbreviations: NSCLC, non – small-cell lung cancer; ORR, objective response rate; SE, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value.

In addition, classic phase II designs may not identify a highly active agent, as exemplified by the recent studies of sorafenib. A randomized discontinuation trial of this kinase inhibitor was conducted in 202 patients with metastatic renal cell cancer (8). Although the objective response rate (by independent review) was only 4%, there was an obvious and highly significant difference in failure-free survival after randomization, which was confirmed in a phase III trial of 800 patients (9). If this drug had been developed using classic criteria, it may never have entered phase III for this indication, given its low response rate.

The solution for moving forward is to design trials for success, not for failure. This requires abandonment of current oncology paradigms for early clinical trials and adoption of generally accepted principles of drug development. These principles have been promulgated by the Food and Drug

Administration (10) and the U.S. Code of Federal Regulations Title 21 Section 312.21 (11), which states, "Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects." Implementation of such new paradigms will require greater attention to trial design issues in both phase I and II, but with the overriding principle that will require larger trials to prove activity. Such change will hopefully lead to a higher success rate in phase III, thereby allowing a more rapid translation of scientific advances into cost-effective therapy for cancer patients.

References

- Goffin J, Baral S, Dongsheng T, Nomikos D, Seymour L. Objective responses in patients with malignant melanoma or renal cell cancer in early clinical studies do not predict for regulatory approval. *Clin Cancer Res* 2005;11:5928–34.
- Chu K. An introduction to sensitivity, specificity, predictive values and likelihood ratios [review]. *Emerg Med* 1999;11:175–81.
- Ratain MJ, Eckhardt SG. Phase II studies of modern drugs directed against new targets: if you are fazed, too, then resist RECIST. *J Clin Oncol* 2004;22:4442–5.
- Booth B, Glassman R, Ma P. Oncology's trials. *Nat Rev Drug Discov* 2003;2:609–10.
- Shen L. An improved method of evaluating drug effect in a multiple dose clinical trial. *Stat Med* 2001;20:1913–29.
- Sheiner LB. Learning versus confirming in clinical drug development. *Clin Pharmacol Ther* 1997;61:275–91.
- Ratain MJ, Mick R, Schilsky RL, Siegler M. Statistical and ethical issues in the design and conduct of phase I and II clinical trials of new anticancer agents. *J Natl Cancer Inst* 1993;85:1637–43.
- Ratain M, Eisen T, Stadler W, et al. Final findings from a phase II, placebo-controlled, randomized discontinuation trial (RDT) of sorafenib (BAY 43–9006) in patients with advanced renal cell carcinoma (RCC). *Proc Am Soc Clin Oncol* 2005;23:388s.
- Onyx Pharmaceuticals [homepage on the Internet]. BAY 43–9006 shown to delay disease progression in phase III study in advanced kidney cancer patients. [cited 2005 Mar 21]. Available from: <http://www.onyx-pharm.com/wt/page/pr.1111376865>.
- Food and Drug Administration [homepage on the Internet]. General considerations for the clinical evaluation of drugs. [issued 1978]. Available from: www.fda.gov/cder/guidance/old034fn.pdf.
- US Government Printing Office-NARA [homepage on the Internet]. Food and Drug Administration, Dept. of Health and Human Services, Code of Federal Regulations. Investigational new drug application. Vol. 21, pp. 54, 2003. Available from: <http://www.access.gpo.gov/cgi-bin/cfrassemble.cgi?title=200021>.

Appendix RATAIN03

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Optimising the design of phase II oncology trials: The importance of randomisation

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ABSTRACT

Oncology trial end-points continue to receive considerable attention, as illustrated by the development and revisions to the RECIST criteria. In this article, we focus the reader away from the issue of end-points for phase II trials and towards what we believe to be an even more important issue, the fundamental need for randomisation in phase II oncology trials, ideally with blinding and dose-ranging. We present arguments to support the proposition that randomisation will enable greater clarity in the interpretation of the phase II trial results, as well as allowing for more precise estimates of the effect size and sample size requirements for definitive phase III trials. Randomisation will also reduce potential bias resulting from inter-trial variability, which inflates both type I and II errors if historical controls are utilised. In the context of a randomised blinded trial, the exact choice of end-point is less critical, although we favour end-points such as the change in tumour size or progression status at a fixed early time point (i.e. 8–12 weeks after randomisation). Although end-points based on RECIST criteria can and should be utilised in randomised phase II trials, we do not believe that revision of the RECIST criteria will result in a fundamental improvement in drug development decisions in the absence of randomised clinical trials at the phase II stage of drug development.

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1. Introduction

The phase II clinical trial plays a central role in oncology drug development. After a phase I trial has determined a tolerable dose for a new agent or combination, a well-designed phase II trial should provide the information required to make a go/no-go decision regarding subsequent phase III testing. As phase III trials require several years, hundreds or thousands of patients and often tens or hundreds of millions of dollars, the information that a quality phase II trial can provide is essential to a decision regarding the potential investment in a larger trial. In this paper, we present a rationale for the ex-

panded use of randomisation in phase II oncology trials, in order to better inform this decision-making process.

2. Why do we do phase II trials?

Phase II trials should be most appropriately viewed as proof of concept trials, used for the purpose of determining whether a particular agent (or combination) should be studied further.¹ In this sense, they serve a critical filtering mechanism, in which a negative trial should lead to the discontinuation of development of a new agent for the selected indication. Optimising the filtering process is the critical issue: too tight

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a filter will terminate promising agents improperly, but a too porous filter will result in an excessive number of costly negative phase III trials. In the previous era of oncology drug development, there were very few drugs available for the study, and as such a porous filter was very appropriate to minimise the possibility that a false-negative result would result in the discarding of a promising agent.

In the current era, there are hundreds of investigational oncology drugs available for the study. As such, we believe that it is more appropriate (at least at a societal level) to use a tighter filter, one that only advances to phase III development of those drugs for which there is a high probability of success in the phase III trial. We recognise that this strategy may be problematic for companies with a single drug in development. However, from a societal view, minimising the number of phase III trials of ineffective agents is important, as patients enrolled on a negative phase III trial may have lost the opportunity to participate in the trials of active investigational agents, and financial and intellectual resources spent on a negative phase III trial similarly would be better spent on the development of new agents. Given the patient and financial resources required for a phase III trial in the current environment, we feel that it is more important to minimise the risk of failing to demonstrate the efficacy in phase III trial than to be concerned about the lost opportunities subsequent to not proceeding to phase III testing.

We propose that attempting to ensure that phase III trials attain success on their specified end-point is best determined through the explicit modelling of the relationship of dose to both efficacy and toxicity. If an identifiable and reliable relationship between dose and the chosen efficacy end-point can be established, considerable evidence is provided in support of the success of the eventual phase III trial, particularly

if that efficacy signal is apparent at doses with an acceptable toxicity. On the other hand, if there is no relationship between dose and efficacy, the drug may either be inactive or be active with a wide therapeutic index (Table 1).

The information required to enable the best determination of dose–efficacy and dose–toxicity relationships is only obtainable from a randomised comparative phase II trial, as a single-arm trial only provides information for a single dose. Furthermore, unless the efficacy end-point is a response rate, it may not even be clear that the drug is efficacious at all, as demonstration of a prolonged period of stable disease may be due to an inadvertent selection of patients with a favourable natural history, independent of any pharmacological drug effect.

A further factor influencing our endorsement of randomised phase II trials is the reality that a decision to move a drug from phase II to III is not a simple ‘thumbs up’ or ‘thumbs down’ decision. The standard phase II single-arm design is based on the promise that a difference of a single success (typically tumour response) determines the phase III go/no-go decision. While even proponents of a single-arm trial likely realise that this is an artificial construct, the lack of randomisation in a single-arm trial hinders the ability to judge the toxicity relative to control, to consider alternate end-points that may be more sensitive to the treatment effect, and to estimate the effect size relative to control that may be expected in the envisioned phase III trial.² These effect sizes are the primary determinant of the sample size (and probability of success) in the phase III trial, and may also impact phase III end-point selection. Drugs may be active but fail in phase III because a phase III trial is too small, or because the chosen dose is too low (or high). Furthermore, it is important to have a fairly robust estimate of the effect size, and the reliability of that estimate is determined by the sample size in phase II. Every one of these factors (effect size, relative toxicity, sensitive end-points and dose–efficacy) is better estimated through a direct randomised comparison at the phase II testing stage.

Table 1 – Impact of randomisation on strength of inference in phase II trial.		
Phase II strategy	Result	Strength of inference
Single-arm trial	Positive signal	Unknown if due to true efficacy or bias
	Negative signal	Unknown if due to lack of efficacy, bias or wrong end-point
Two-arm randomised trial with no control	Positive signal	Some sign that one agent more promising than another, but overall efficacy unclear
	Negative signal	Unknown if due to lack of efficacy, bias or wrong end-point
Two-arm randomised trial with control	Positive signal	Strong efficacy signal, but dosing may not be optimised
	Negative signal	Dose ineffective
Multiple-arm randomised trial with control	Positive signal	Strong efficacy signal, dosing able to be optimised
	Negative signal	Drug ineffective

3. What are the options for design of phase II trials?

Historically, phase II oncology trial designs can be divided into three categories: non-randomised (single-arm) trials compared to historical controls, randomised trials with multiple-experimental regimens compared to a historical control, and randomised trials including a prospective control arm. In this section, we provide a brief overview of each of these design strategies.

The single-arm trial has been the most frequently used approach to the efficacy evaluation at the phase II level in oncology, although it should be emphasised that this approach is rarely used in other therapeutic areas. Although there are multiple approaches to the implementation of the single-arm design, the overall principle has changed little since the design of Gehan.³ Patients are typically enrolled in two stages. If sufficient activity is observed at the end of the first stage, accrual continues to a second stage, and the number of successes (typically tumour responses) at the trial’s conclusion determines whether the agent is ‘recommended’ for further testing. Multiple variations, including optimal selection of

interim analysis time points, additional stages of accrual, considerations for multiple end-points, Bayesian approaches and approaches allowing three possible outcomes have been proposed.^{4–8} In an era when most new anticancer agents had very limited efficacy and thus any evidence of tumour activity was sufficient to warrant future testing, the single-arm design provided a simple, direct and rapid method to assess an agent's activity. The fundamental assumptions underlying the single-arm phase II trial are that data from the previous studies provide an adequately robust estimate of the experience the patients from the current trial would have had were they not to have received the experimental therapy, and that the end-point selected for the trial represents a definitive measure of agent activity. Both these assumptions are suspect in the current era. Rapidly changing standards of care in many diseases in therapy, imaging and supportive care imply that historical data may not be reflective of the results observed in the current clinical practice. This is compounded by the fact that advances in tumour biology are segregating disease into marker-specific subtypes (e.g. based on Her-2 or K-ras status), for which historical data may be totally absent. In addition, new agents with novel mechanisms of action imply that standard end-points, such as tumour response, may not accurately capture an agent's overall patient benefit. The combination of these factors, in our opinion, questions the appropriateness of the single-arm trial at a fundamental level.

A second class of phase II trials includes a randomisation to two or more experimental arms, but no prospective control arm. The goal of such a trial, often referred to as a selection design, is to provide more robust data than are available through single-arm trials to select the most promising experimental regimen to compare to a prospective control in the phase III setting. Numerous potential options for such trials have been proposed,^{9–11} all of which rely on an implicit comparison to historical controls in terms of the level of activity required to justify moving forward the most promising experimental regimen to the phase III setting. As these phase II trials are not designed to establish a new standard of care, little concern is paid to the true type I error (the false-positive rate), which generally does not account for the multiplicity of testing (through multiple-experimental arms), as well as to an error in the implicit historical control. While these selection designs do clearly provide much stronger comparative data to select a promising regimen amongst many possible phase III trials, the implicit comparison to historical controls confers the same disadvantages previously specified for the single-arm phase II trial.

The third class of phase II trials includes a randomisation to one or more experimental arms and a prospective control arm. This is the standard approach to drug development in other therapeutic areas, in which the phase II programme is often divided into phase IIa (a two-arm trial for proof of concept) followed by phase IIb (a dose-ranging trial to optimise the phase III design). Two sub-classes of these randomised controlled designs have been used: those that formally use the control arm in the efficacy determination, and those that use the control informally. In the latter design, the control arm data are assessed as to its similarity to historical controls; if the control arm produces results that are 'similar' to prior experience, then the results from the experimental

arm are considered valid. In our opinion, the inclusion of an 'informal' control arm serves a false purpose. These trials are inherently comparative, and if it is recognised that the go/no-go decision for phase III testing will be based on many factors and will not be dependent on traditional statistical significance ($p < 0.05$), then to ignore the power of randomisation to allow direct between-arm comparisons serves no valid scientific purpose. If the control arm is used in a formal efficacy comparison, the method of comparison is similar to that of a phase III trial, such as using a chi-squared comparison of response rates, or a log-rank comparison of progression-free survival (PFS) times. The formal use of the control group in the efficacy comparisons has been discussed by Rubinstein et al.,¹² Fleming and Richardson¹³ and others.

4. When is a non-randomised phase II trial sufficient?

We believe non-randomised phase II trials in oncology should be the exception, not the rule. With that caveat, we acknowledge that such trials may be appropriate for trials in which the desired outcome (e.g. a partial response) will not occur in the absence of the investigational agent, and the rate of that outcome for existing agents or regimens is historically highly reliable. In this context, a positive phase II trial, defined as a response rate greater than some predefined threshold, would be evidence for activity, and a negative phase II trial would lead to the discontinuation of development for the specific indication.

Importantly, these criteria would never be met by many end-points often used in oncology clinical trials, such as 'clinical benefit or survival beyond some threshold (unless that threshold was inconsistent with the natural history of the disease)'. In addition, combination trials would generally not meet these criteria, unless the non-investigational components of the combination were known to be inactive in the target patient population. Finally, given the currently rapidly changing standards of care in many disease, once a new 'standard' has been defined in any given disease, the historical data obtained to date are invalid, due both to the availability of the new standard, and the fact that a new standard may change the treatment paradigm in that disease (e.g. poor prognosis patients who were previously untreated, thus not included in the historical control rates, may now become part of the treatment population).

Additionally, non-randomised trials should never be used if there is an uncertainty regarding the optimal dose. The maximally tolerated dose has been traditionally utilised for phase II evaluation, despite the clear evidence against the general validity of the 'more is better' paradigm.¹⁴ For example, the randomised dose-ranging phase II trial of temsirolimus in renal cell cancer showed that doses of 25, 75 and 250 mg weekly were all equally effective, leading to a successful phase III trial at the lowest dose.^{15,16}

We acknowledge that many experienced investigators continue to advocate the utility response rate as assessed in single-arm phase II trials. El-Maraghi and Eisenhauer¹⁷ reviewed 89 trials of 19 agents, and concluded that the observation of objective responses predicted for an eventual success.

Given that the drugs with a 0% response rate in a single-arm phase II trial would not proceed to phase III testing, it is not surprising that no such agent achieved FDA approval. On the other hand, four of the six agents with the response rates under 10% were approved, including two agents with the response rates of less than 5% as single agents (cetuximab and sorafenib). The authors concluded that ‘even low levels of response may be interesting’ and acknowledged that larger phase II trials are required. However, the authors do not discuss an important implication of their recommendation, which is likely the further increase in the number of phase III trials that will fail to achieve their desired end-point if all the drugs with the response rates of 3–4% (as observed with cetuximab and sorafenib) underwent phase III testing. We feel that PFS provides a superior signal from which to assess the efficacy for such agents, which is clearly assessed optimally through a randomised trial.

Some authors have also suggested that the utility of single-arm trials using PFS or overall survival rates at a predefined landmark could be improved through the use of a model-based, comparison to historical controls. One example is a recent study by Korn and colleagues from five cooperative groups¹⁸ where the authors reported a multivariate prognostic model for metastatic melanoma, which they proposed could be utilised in single-arm phase II trials, as an alternative to randomised trials. They suggest that only 63 patients would be required in a single-arm trial in this setting to have the same type I and II errors as a 220 patient randomised trial. While this model-based approach likely does provide some improvement compared to an unadjusted comparison to historical controls, it does not change our fundamental belief in the value of randomization: unless the model is perfect (which it never is), it is impossible to fully adjust the type I and II error for inter-trial variability, which in our opinion is the primary reason that single-arm phase II results are not replicated in phase III trials, as discussed further in the next section.

5. When does a non-randomised phase II trial lead to a phase III trial that fails to achieve success on its primary end-point?

As stated previously, the fundamental assumptions that could justify a single-arm phase II trial are that data from the previous studies provide an adequately robust estimate of the experience of the treated patients from the current trial were they not to have received the experimental therapy, and that the end-point selected for the trial represents a definitive measure of agent activity. Not surprisingly, when these assumptions are violated (which is common), phase III trials have a high rate of failing to demonstrate a significant improvement in the primary end-point from the experimental therapy.

From our perspective, the single greatest reason that uncontrolled phase II trials generate ‘false’ hope is the inter-trial variability in end-point success rates. Statistically, the failure to acknowledge the variability in the historical success rate inflates the nominal type I error level in the uncontrolled phase II trial.¹⁹ More importantly, regardless of the trial’s end-

point, rapid advances in treatment outside the study protocol, supportive care, imaging modalities (to assess disease status) and other factors imply that patient outcomes will likely improve over time regardless of any new therapy. A likely even more dominant factor in the overall patient level success rate for a trial is the institutional composition of enrolling physicians and sites. Patient outcome has been repeatedly shown to associate with physician volume, and the patient mix at academic medical centres (which conduct the majority of phase II trials) differs widely from that in community practice. These three factors (statistical underestimation, patient outcome drift and patient selection) combine to make the true type I error rate for the primary end-point in uncontrolled phase II trials completely unknown (and unknowable).

Multiple additional factors contribute to difficulty in predicting successful phase III trials based on single-arm phase II trials. In single-arm trials of drug combinations, it is very difficult to distinguish the relative contribution of the standard component from the experimental agent. The choice of a different end-point in a phase II trial (such as tumour response) compared to phase III (where overall survival or PFS is likely to be primary) is problematic, as response rate has been repeatedly shown to be a poor surrogate for these time-to-event end-points.

The use of a control arm in a two-arm randomised phase II trial, comparing a single experimental regimen to a control, alleviates many of the issues above; however, several problematic issues remain. As regimen doses and schedules are typically established through small phase I trials, with few (typically <12) patients treated at the MTD, limited information is available in most cases on the dose–efficacy and dose–toxicity relationships for the new agent. One potential cause of the failure in phase III trials is the error in the dose – either too high resulting in an unacceptable toxicity or too low resulting in an inadequate efficacy. This risk can be minimised with a multiple-arm randomised phase II trial, where several dose levels are explored initially, and adaptively removed from the trial based on prespecified criteria.²⁰

6. What are the considerations in the design of randomised phase II trials?

Although there has been a debate about the value of formal statistical comparisons in phase II trials, we feel strongly that such comparisons are appropriate, with the caveat that phase II trials do not necessarily need to provide reliable definitive comparisons at a traditional two-sided type I error of 0.05. Given that the purpose of any phase II trial is to determine whether to proceed with further agent development, there is only one outcome of interest, superiority of one or more experimental arms to the control. In this scenario, we believe a one-sided testing framework is appropriate. Given the need for phase II trials to be as small as possible and that a phase III trial will be required to confirm the efficacy in most cases, standard type I error rate control at the 0.05 level is not necessary. We and others¹² propose that a one-sided test of the null hypothesis that the true primary outcome is no different between treatment and control with a false-positive rate of 0.20 (type I error) is appropriate. In theory, if every phase III

trials were required to be justified by a randomised phase II trial with $p < 0.20$, this would lead to a phase III success rate of 80%, a significant improvement from the status quo. In contrast, in the uncontrolled phase II setting, the true false-positive rate is unknown.

The use of this higher type I error remedies one common criticism of randomised phase II trials, that of very low statistical power.²¹ In the case of a multiple-experimental arm phase II randomised trial with a control, appropriate type I error control is necessary to maintain an overall type I error rate of 20%, either through adjusting the alpha level for each comparison of control versus treatment, or by comparing the experimental treatments to each other to identify the best, then comparing that regimen to control. Sample size considerations typically also dictate a type II error rate of 0.20, for a modest effect size (e.g. a hazard ratio of 1.5 in a time-to-event end-point, or a difference in response rates of 15–20%), although a lower type I and II error rates (e.g. 0.10) should also be considered if resources allow.¹²

The choice of primary end-point in a randomised phase II trial depends on multiple factors. Ideally, a phase II screening trial should be as similar as possible to the subsequent phase III trial, including choice of primary end-point. Given the movement in advanced disease trials towards PFS as a phase III primary end-point,²² this is increasingly possible. Although overall survival can also be considered as the primary end-point for phase II and/or III testing, this would not permit the use of crossover designs, especially useful in the phase II setting.

In our opinion, the most promising end-points for randomised phase II trials involve a comparison of a primary outcome measure at a single time point between the treatment and control groups. This outcome measure could be a tumour assessment at a fixed time point (e.g. change in absolute tumour size from baseline at 8–12 weeks following treatment initiation), or a rate of overall survival or PFS at a fixed time point (for example, 3 or 6 months). Such end-points facilitate independent radiologic review, eliminate subtle differences in scanning frequencies, simply patient scheduling and can be chosen to represent clinically meaningful time points. Ongoing research in multiple disease areas is examining these and other end-points to identify which end-points optimally predict phase III success. In the future, newer methods such as functional imaging or assessment of circulating tumour cells may allow even earlier assessment of disease status.

The validity of almost all end-points is improved by blinding, a tool infrequently used in oncology trials, particularly phase II trials. This is less important when overall survival is the primary end-point, but critical for end-points such as PFS, since independent radiological review can address bias in measurement but not bias in timing of radiological studies. When a trial is blinded, one can consider the use of novel end-points that incorporate patient-reported outcomes (e.g. time to symptomatic progression). In addition, blinding will result in a more robust analysis of toxicity attributable to the investigational agent, as it controls for the 'placebo effect'. Blinding can be logistically complicated, as it requires the availability of either an indistinguishable placebo (for oral agents) or sham parenteral dosing (for intravenous or subcutaneous agents). Although we feel that blinding should be considered

for all randomised comparative phase II trials, we acknowledge that the final decision must consider all of these issues.

The use of blinding also permits the use of the randomised discontinuation (or withdrawal) design, in which all eligible patients initially receive active treatment for a predefined run-in period. In this design, patients with stable disease at the end of a run-in period proceed to the randomised portion of the study (the primary analysis), in which they are randomised to continued active treatment or placebo. To minimise the risk to patients randomised to the placebo arm, all patients are offered crossover at progression, and those patients who had been randomised to placebo are restarted on open-label active treatment (those patients who had been randomised to active treatment are withdrawn). This design is particularly useful for the trials of the new agents as a single agent where it is hypothesised that the response rate is low, but that the drug has a clinically significant antitumour effect. We strongly feel that this design is superior in this setting to the use of a large single-arm trial, as a positive trial demonstrating a low response rate does not provide sufficient information to inform a robust decision to proceed to phase III testing.

7. Conclusions

Randomisation is greatly underutilised in early clinical trials in oncology. The use of randomised trials allows complete flexibility in the choice of end-points, particularly if blinding can be incorporated. This technique is the most powerful and reliable technique for distinguishing the effect of a drug from a placebo, a necessary predicate for a successful phase III trial. Given the large number of agents now available for clinical testing, the costs of phase III trials, and the limited patient and financial resources, available for such testing, the increased use of randomised phase II trials provides a rational way to move new agents forward. Although end-points based on RECIST criteria can and should be utilised in randomised phase II trials, we do not believe that revision of the RECIST criteria will lead to any fundamental impact on improving drug development decisions in the absence of randomised clinical trials at the phase II stage of the drug development.

Conflict of interest statement

None declared.

REFERENCES

1. Sheiner LB. Learning versus confirming in clinical drug development. *Clin Pharmacol Ther* 1997;**61**(3):275–91.
2. De Ridder F. Predicting the outcome of phase III trials using phase II data: a case study of clinical trial simulation in late stage drug development. *Basic Clin Pharmacol Toxicol* 2005;**96**(3):235–41.
3. Gehan EA. The determination of the number of patients required in a preliminary and a follow-up trial of a new chemotherapeutic agent. *J Chronic Dis* 1961;**13**:346–53.

4. Bryant J, Day R. Incorporating toxicity considerations into the design of two-stage phase II clinical trials. *Biometrics* 1995;**51**(4):1372–83.
5. Chang MN, Therneau TM, Wieand HS, Cha SS. Designs for group sequential phase II clinical trials. *Biometrics* 1987;**43**(4):865–74.
6. Sargent DJ, Chan V, Goldberg RM. A three-outcome design for phase II clinical trials. *Control Clin Trial* 2001;**22**(2):117–25.
7. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trial* 1989;**10**(1):1–10.
8. Thall PF, Simon R. Practical Bayesian guidelines for phase IIB clinical trials. *Biometrics* 1994;**50**(2):337–49.
9. Sargent DJ, Goldberg RM. A flexible design for multiple armed screening trials. *Stat Med* 2001;**20**(7):1051–60.
10. Schaid DJ, Ingle JN, Wieand S, Ahmann DL. A design for phase II testing of anticancer agents within a phase III clinical trial. *Control Clin Trial* 1988;**9**(2):107–18.
11. Simon R, Thall PF, Ellenberg SS. New designs for the selection of treatments to be tested in randomized clinical trials. *Stat Med* 1994;**13**(5–7):417–29.
12. Rubinstein LV, Korn EL, Freidlin B, Hunsberger S, Ivy SP, Smith MA. Design issues of randomized phase II trials and a proposal for phase II screening trials. *J Clin Oncol* 2005;**23**(28):7199–206.
13. Fleming TR, Richardson BA. Some design issues in trials of microbicides for the prevention of HIV infection. *J Infect Dis* 2004;**190**(4):666–74.
14. Winer EP, Berry DA, Woolf S, et al. Failure of higher-dose paclitaxel to improve outcome in patients with metastatic breast cancer: cancer and leukemia group B trial 9342. *J Clin Oncol* 2004;**22**(11):2061–8.
15. Atkins MB, Hidalgo M, Stadler WM, et al. Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. *J Clin Oncol* 2004;**22**(5):909–18.
16. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007;**356**(22):2271–81.
17. El-Maraghi RH, Eisenhauer EA. Review of phase II trial designs used in studies of molecular targeted agents: outcomes and predictors of success in phase III. *J Clin Oncol* 2008;**26**(8):1346–54.
18. Korn EL, Liu PY, Lee SJ, et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. *J Clin Oncol* 2008;**26**(4):527–34.
19. Thall PF, Simon R. Incorporating historical control data in planning phase II clinical trials. *Stat Med* 1990;**9**(3):215–28.
20. Inoue LY, Thall PF, Berry DA. Seamlessly expanding a randomized phase II trial to phase III. *Biometrics* 2002;**58**(4):823–31.
21. Liu PY, LeBlanc M, Desai M. False positive rates of randomized phase II designs. *Control Clin Trial* 1999;**20**(4):343–52.
22. Sargent DJ, Hayes DF. Assessing the measure of a new drug: is survival the only thing that matters? *J Clin Oncol* 2008;**26**(12):1922–3.

Appendix RATAIN04

Dose-Finding and Pharmacokinetic Study to Optimize the Dosing of Irinotecan According to the *UGT1A1* Genotype of Patients With Cancer

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See accompanying editorial on page 2287

ABSTRACT

Purpose

The risk of severe neutropenia from treatment with irinotecan is related in part to *UGT1A1**28, a variant that reduces the elimination of SN-38, the active metabolite of irinotecan. We aimed to identify the maximum-tolerated dose (MTD) and dose-limiting toxicity (DLT) of irinotecan in patients with advanced solid tumors stratified by the *1/*1, *1/*28, and *28/*28 genotypes.

Patients and Methods

Sixty-eight patients received an intravenous flat dose of irinotecan every 3 weeks. Forty-six percent of the patients had the *1/*1 genotype, 41% had the *1/*28 genotype, and 13% had the *28/*28 genotype. The starting dose of irinotecan was 700 mg in patients with the *1/*1 and *1/*28 genotypes and 500 mg in patients with the *28/*28 genotype. Pharmacokinetic evaluation was performed at cycle 1.

Results

In patients with the *1/*1 genotype, the MTD was 850 mg (four DLTs per 16 patients), and 1,000 mg was not tolerated (two DLTs per six patients). In patients with the *1/*28 genotype, the MTD was 700 mg (five DLTs per 22 patients), and 850 mg was not tolerated (four DLTs per six patients). In patients with the *28/*28 genotype, the MTD was 400 mg (one DLT per six patients), and 500 mg was not tolerated (three DLTs per three patients). The DLTs were mainly myelosuppression and diarrhea. Irinotecan clearance followed linear kinetics. At the MTD for each genotype, dosing by genotype resulted in similar SN-38 areas under the curve (AUCs; $r^2 = 0.0003$; $P = .97$), but the irinotecan AUC was correlated with the actual dose ($r^2 = 0.39$; $P < .001$). Four of 48 patients with disease known to be responsive to irinotecan achieved partial response.

Conclusion

The *UGT1A1**28 genotype can be used to individualize dosing of irinotecan. Additional studies should evaluate the effect of genotype-guided dosing on efficacy in patients receiving irinotecan.

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INTRODUCTION

Irinotecan is an active agent in the treatment of several solid tumors. Its pharmacology has been studied for the last 20 years, and the key pathways for irinotecan disposition have been well described. Because irinotecan is a prodrug, its activation to the potent metabolite SN-38 is required for both antitumor activity and the mechanism-related toxicities of the drug, especially neutropenia. The relative importance of intratumoral activation to SN-38, versus hepatic activation, is still unknown. Patients treated with irinotecan have marked variability in toxicity at standard doses.¹

*UGT1A1**28 is a biomarker of neutropenia that is mentioned in the irinotecan package insert. This germline genetic variant results in reduced expression of *UGT1A1*, the main metabolizing enzyme that inactivates SN-38 through glucuronidation to SN-38 glucuronide (SN-38G).² In several studies, the variability in systemic exposure to SN-38 has been associated with the risk of neutropenia.³⁻⁶ Thus, the presence of *UGT1A1**28 could be an indicator of a patient's risk of myelosuppression.^{4,7,8} According to the package insert,⁹ a reduced first dose of irinotecan should be considered in patients homozygous for this allele (*28/*28), but the extent of dose reduction is not indicated. Whether the

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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standard dose of irinotecan is appropriate for patients who do not have the *28/*28 genotype remains to be established.

Despite the known variability in irinotecan disposition, the drug is still dosed according to body surface area (BSA), a strategy without a pharmacologic rationale. Because *UGT1A1**28 is associated with the risk of irinotecan-related myelosuppression, a phase I study of single-agent irinotecan in patients with refractory cancer was designed to find the safe doses of irinotecan according to the *UGT1A1**28 genotypes of patients. We hypothesized that patients with the *1/*1 genotype would tolerate a higher dose than the standard dose and that patients with the *28/*28 genotype would require dose reduction.

PATIENTS AND METHODS

Patient Eligibility

Patients with histologically confirmed solid tumors or lymphoma refractory to standard therapy were enrolled. Eligibility criteria included *UGT1A1* *1/*1, *1/*28, and *28/*28 genotypes (patients carrying the rare *UGT1A1**36 and *UGT1A1**37 alleles captured by the assay were not eligible); Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; measurable or assessable disease; life expectancy greater than 3 months, age 18 years or older; leukocyte count greater than 3,000/ μ L; absolute neutrophil count (ANC) at least 1,500/ μ L; platelet count at least 100,000/ μ L; total bilirubin within normal institutional limits; ALT and AST levels at less than 2.5 times the upper limit of normal; and a serum creatinine level within normal institutional limits or a glomerular filtration rate greater than 50 mL/min/1.73 m² for patients with creatinine levels above institutional normal as calculated by the modified Modification of Diet in Renal Disease equation recommended by the National Kidney Disease Education Program.

Study Objectives

The primary objective was to describe the maximum-tolerated dose (MTD) and dose-limiting toxicity (DLT) of irinotecan in patients with the *1/*1 and *1/*28 genotypes with advanced solid tumors. Secondary objectives included finding the safe dose of irinotecan in patients with the *28/*28 genotype, evaluating the pharmacokinetics of irinotecan and its metabolites, and describing the antitumor response to irinotecan when doses are given according to genotype. The institutional review board of the University of Chicago and NorthShore University Health System approved the study, and each patient signed a written informed consent form before entering the study.

Drug Administration and Dose Escalation

Irinotecan was administered every 3 weeks by intravenous infusion during 90 minutes. In patients with the *1/*1 and *1/*28 genotypes, the starting dose was 700 mg (flat dose equivalent to 390 mg/m², according to a BSA of 1.8 m²).¹⁰ In patients with the *28/*28 genotype, the starting dose was 500 mg (ie, 280 mg/m²). BSA has not been shown to be a predictor of irinotecan pharmacokinetic variability.¹¹ Planned dose escalation in the patients with the *1/*1 and *1/*28 genotypes was by increments of 150 mg.

DLT at cycle 1 was defined as grade 4 neutropenia lasting $\geq$ 4 days, grade 3 or higher neutropenia on a scheduled treatment day, grade 3 or higher febrile neutropenia, grade 4 anemia or thrombocytopenia, grade 3 or higher diarrhea despite administration of loperamide therapy, grade 3 or higher nonhematologic toxicity, or grade 4 nausea or nausea/vomiting graded by the National Cancer Institute Common Toxicity Criteria, version 3.0.

One treatment cycle was 21 days. Before starting irinotecan, patients were pretreated with ondansetron 16 mg. Diarrhea was treated promptly with loperamide 4 mg at the onset and then with 2 mg every 2 hours, until the patient was diarrhea free for at least 12 hours. Hematopoietic growth factors (eg, granulocyte colony-stimulating factor) and other supportive care measures were administered when deemed clinically appropriate by the treating physician. Atropine 0.25 to 1 mg was administered in case of acute cholinergic syndrome.

The planned dose escalation was to enroll six patients at each dose level and to continue escalating if fewer than two of the six patients experienced DLT. If two or more of the six patients experienced DLT, the dose was declared above the MTD. The next-lower dose level then was expanded to up to 12 patients; if fewer than four of the 12 patients experienced DLT, this dose level was declared the MTD. No inpatient dose escalation was allowed. In some cohorts, more than 12 patients were enrolled to adequately assess the tolerability of the dose level.

Pharmacokinetics of Irinotecan and *UGT1A1**28 Genotyping

We evaluated the pharmacokinetics of irinotecan and metabolites during cycle 1. Serial blood samples were collected into heparinized tubes before drug administration; at 30 minutes; and at 1, 1.5, 1.7, 1.8, 2, 2.25, 2.5, 3, 3.5, 5.5, 6.5, 7.5, 8.5, and 25.5 hours after the start of the irinotecan infusion. The pharmacokinetics of irinotecan and its metabolites SN-38 and SN-38 glucuronide (SN-38G) were determined as previously described¹² by using noncompartmental analysis (PK Solutions Software, version 2.0, Summit Research Services, Montrose, CO). Estimated parameters included the area under the concentration-time curve from 0 to infinity ($AUC_{0-\infty}$), clearance (calculated as dose $\div$ AUC), and glucuronidation ratio (calculated as $AUC_{SN-38G} \div AUC_{SN-38}$). *UGT1A1**28 genotyping from DNA extracted from peripheral blood was conducted as previously reported.¹³

Efficacy and Toxicity Assessment

Clinical examination and hepatic and renal function tests were performed at baseline and within 48 hours before each irinotecan administration. Computed tomography scans of measurable lesions were assessed at baseline and then repeated every two cycles. Objective tumor response was evaluated every two cycles according to the RECIST criteria,¹⁴ and patients who experienced progression before two cycles were not evaluable for tumor response. Blood counts were measured at baseline, weekly during cycle 1, and within 48 hours before each treatment administration in the following cycles. If a patient had grade 4 neutropenia, the blood counts were repeated daily until resolution occurred to determine whether grade 4 neutropenia was a DLT.

Patients were treated at the protocol-specified full dose of irinotecan if the laboratory entry criteria were met before each cycle. Any patient who experienced grade 3 or greater toxicity attributable to therapy had treatment held until toxicity resolved to grade 1 or lower. Patients who experienced DLT were treated at the next-lower dose for their genotype (in cycle 2) as long as there was no evidence of progressive disease. Irinotecan was discontinued because of disease progression, patient refusal, or physician recommendation.

Statistical Methods

The MTD for each genotype was determined as described above. Exploratory analyses were conducted on the secondary objectives of the study, and $P < .05$ was considered statistically significant. The nonparametric Kruskal-Wallis test and analysis of variance were used for group comparisons; these agreed closely, and only the nonparametric results are reported here. Multiple linear regression models were fit to examine the association between ANC nadir and dose, sex, genotype, and pharmacokinetic variables.

RESULTS

Patients, Genotypes, and Dose Range

Sixty-eight patients were assessable for DLT (Table 1). Most patients were men and white. The prevalent tumor types were GI and lung. The distribution of the *UGT1A1* genotypes was 31 *1/*1, 28 *1/*28, and nine *28/*28 ($P > .05$ for the Hardy Weinberg equilibrium). The genotype frequency followed the expected distribution of *UGT1A1**28 in populations of European origin. The dose levels of irinotecan administered to patients ranged from 400 to 1,000 mg (flat dose; Table 2).

Table 1. Patient Characteristics

Characteristic	No.	%
No. of evaluable patients		
Enrolled	68	
Assessable for toxicity	68	
Assessable for pharmacokinetics	67	
Assessable for tumor response†	48	
Age, years		
Median	63	
Range	35-80	
Sex		
Male	45	66
Female	23	34
Ethnicity		
White	56	82.4
Black	9	13.2
Hispanic	3	4.4
Body surface area, m ²		
Median	1.9	
Range	1.4-2.4	
Previous chemotherapy		
Yes	66	97
No	2	3
ECOG PS		
0	27	39.7
1	40	58.8
2	1	1.5
Tumor type‡		
Gastrointestinal	30	44
Lung	30	44
Other	8	12
UGT1A1*28 genotype§		
*1/*1	31	46
*1/*28	28	41
*28/*28	9	13

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

†Twenty patients were not assessed for response, because they were taken off study during cycle 1. One patient had only three blood draws and, therefore, could not undergo pharmacokinetic evaluation.

‡Other tumor types included breast, maxillary sinus, endocrine, thymic carcinoid, carcinoid, and Merkel cell.

§The UGT1A1*28 genotypes did not deviate from the Hardy-Weinberg equilibrium ($P \geq .05$).

Assessment of MTD and DLT by Genotype

In patients with the *28/*28 genotype treated at the starting dose of 500 mg, three DLTs were observed in three patients, and no additional patients were enrolled at this dose level. The protocol subsequently was amended to treat the patients with the *28/*28 genotype at 400 mg, and one DLT was observed in six patients. The MTD in patients with the *28/*28 genotype, therefore, was determined to be 400 mg.

In patients with the *1/*28 genotype, two DLTs were observed in six patients treated at 850 mg (in addition to two grade 3 nausea and/or vomiting subsequently amended not to be considered as DLTs). Because five DLTs were observed in 22 patients treated at 700 mg, the MTD in patients with the *1/*28 genotype was determined to be 700 mg.

In patients with the *1/*1 genotype, one DLT was observed in nine patients treated at 700 mg. Two DLTs were observed in six men treated at 1,000 mg. At 850 mg, only two of 11 men experienced DLT,

whereas two of five women experienced DLT. The protocol, therefore, was amended to escalate the irinotecan dose to 1,000 mg only in men; two of these six patients experienced DLT. Because, four DLTs were observed overall in 16 patients treated at 850 mg, the MTD in patients with the *1/*1 genotype was determined to be 850 mg.

As summarized in Table 2, the predominant DLT was myelosuppression, with neutropenic DLTs accounting for 75% of DLTs (16 of 20) and severe diarrhea accounting for 25% of DLTs (five of 20). One patient (a man with lung cancer, *1/*28 genotype, and treatment at 850 mg) died as a result of complications of pneumonia (regarded as probably related to treatment) in the presence of grade 4 neutropenia.

Pharmacokinetics of Irinotecan and Antitumor Activity

Sixty-seven patients were assessable for pharmacokinetics. In the 400 to 1,000 mg dose range, irinotecan clearance followed linear kinetics (Table 3). SN-38 AUC displayed the same linear behavior (results not shown). As expected, dose-adjusted irinotecan AUC was independent of the UGT1A1*28 genotype ($P = .62$), whereas dose-adjusted SN-38 AUC increased if patients had the *1/*28 or *28/*28 genotype relative to those with the *1/*1 genotype ($P = .01$; Fig 1).

The MTD was 850 mg in patients with the *1/*1 genotype, 700 mg in those with the *1/*28 genotype, and 400 mg in those with the *28/*28 genotype. Individualizing dose by genotype resulted in similar mean SN-38 AUCs across all MTDs ($r^2 = 0.0003$; $P = .97$; Fig 2). Conversely, at the MTD for each genotype, irinotecan AUC increased significantly with dose ($r^2 = 0.39$; $P < .001$; Fig 2).

After 28 patients had been enrolled, an interim analysis was performed, and a multivariable model for ANC nadir that included dose, genotype, sex, BSA, and SN-38 AUC was developed. Both SN-38 AUC and sex were associated with ANC nadir ($P < .01$). By using the complete data from the study, this model ($r^2 = 0.24$) also detected a significant effect of SN-38 AUC ($r^2 = 0.14$; $P = .001$) but only a trend for sex ($r^2 = 0.01$; $P = .098$), which suggests lower nadirs for women compared with men; dose and genotype were not statistically significant.

Forty-eight patients were assessable for antitumor response. Four partial responses were observed in patients with non-small-cell lung cancer (700 mg and *1/*28 genotype), gastric cancer (850 mg and *1/*1 genotype), small bowel cancer (850 mg and *1/*28 genotype), and small-cell lung cancer (850 mg and *1/*1 genotype).

DISCUSSION

The current landscape of early drug development is changing, and selecting patients by predictive biomarkers is becoming a common practice to reduce the size of trials and achieve end points faster and at a lower cost. Dose-finding studies should be guided by genetic markers of safety, because they can effectively optimize and tailor dosing. To our knowledge, this is the first single-agent, phase I study that has used germline genetics to individualize dosing of a cancer therapy. This study represents a model for performing genotype-directed safety studies with genetic information. These results remind us about the importance of the germline constitutive genome as the basis for dosing and the risk of adverse reactions, because there are clearly subgroups of patients that tolerate different doses of drug therapies.¹⁵ If these results are taken in the context of the various cancer genome sequencing

Table 2. Dose Escalations and DLTs by Dose Level and *UGT1A1**28 Genotype

Irinotecan Dose, mg†	Total No. of Patients	*1/*1 Genotype			*1/*28 Genotype			*28/*28 Genotype		
		No. of DLTs	Type of DLT	No. of Patients	No. of DLTs	Type of DLT	No. of Patients	No. of DLTs	Type of DLT	No. of Patients
400	6	—			—			1	G3 neutropenic fever	6
500	3	—			—			3	G3 infection, G4 neutropenia > 4 days, G3 diarrhea	3
700	31	1	G4 neutropenia > 4 days and G3 diarrhea	9	5	G4 neutropenia (n = 2), G3 (n = 2) or G4 (n = 1) febrile neutropenia	22	—		
850	22	4	G3 febrile neutropenia (n = 2), G4 febrile neutropenia and G4 diarrhea, G4 neutropenia > 4 days	16	4	G3 nausea, G3 nausea and vomiting, G5 neutropenia, G4 neutropenia > 4 days and thrombocytopenia	6	—		
1,000‡	6	2	G3 diarrhea and febrile neutropenia, G3 diarrhea and G4 neutropenia > 4 days	6	—			—		

Abbreviations: DLTs, dose-limiting toxicities; G, grade.

†Flat dose.

‡All patients who received 1,000 mg were men.

efforts,¹⁶⁻¹⁸ it is likely that somatic genetic markers will direct treatment selection and that germline genetic also might contribute to determination of resistance and safe administration doses, in a truly individualized approach.

For irinotecan, we demonstrated that three distinct groups of patients can be identified according to the common variant *UGT1A1**28 and that the tolerable doses of irinotecan range from 400 to 850 mg. This is a difference of more than two-fold; the ability of the genotype to predict dosing of a cytotoxic agent is remarkable. We also demonstrate that the toxicity profile of individualized irinotecan dosing does not change. Neutropenia is the dominant DLT, and diarrhea contributes to a lesser extent. This is expected, as these adverse effects are likely pharmacodynamic consequences of higher exposure to SN-38, which is in part determined by the *UGT1A1**28 variant.³⁻⁶ Our results conclusively identify its role as a major determinant of safe dosing of irinotecan.

The patients with the homozygous *28/*28 genotype are at the highest risk of toxicity, particularly at the higher doses of irinotecan⁸

used in the schedule of administration once every 3 weeks. Pre-emptive genotyping of *UGT1A1**28 is not commonly performed to identify these patients, because most guidelines (including the package insert) do not clearly indicate the extent to which the dose should be reduced.² In the patients with the *28/*28 genotype in this trial, a 20% dose reduction to 500 mg (the equivalent of 278 mg/m²) is not safe: All three patients treated at this dose level experienced a DLT. Instead, a 40% dose reduction to 400 mg (220 mg/m²) seemed to be tolerated (only one grade 3 **neutropenic fever** among six treated patients; Table 2). In the FOLFIRI regimen (irinotecan with infusional fluorouracil and leucovorin), a 30% dose reduction appears safe for patients with the *28/*28 genotype.¹⁹ Our study, for the first time to our knowledge, provides information about the safe doses of irinotecan in the every-3-week regimen in the patients with the highest risk of severe toxicity.

Patients with the *1/*1 and *1/*28 genotypes represent approximately 90% of the European population.²⁰ In this study, patients with the *1/*28 genotype tolerated 700 mg (390 mg/m²), a dose higher than the standard 350 mg/m². We also observed that patients with the *1/*1

Table 3. Pharmacokinetic Parameters of Irinotecan, SN-38, and SN-38G

Dose, mg	No. of Patients	Irinotecan AUC _{0-∞} (h · mg/L)		Irinotecan CL (L/h)		SN-38 AUC _{0-∞} (h · mg/L)		SN-38G AUC _{0-∞} (h · mg/L)		GR	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
400	6	17.8	4.7	24.2	8.4	0.867	0.708	1.37	0.59	2.63	1.95
500	3	35.0	17.3	18.4	12.7	1.196	0.662	3.41	2.19	2.65	0.61
700	30	33.8	11.8	23.3	8.5	0.808	0.655	2.76	1.96	5.17	5.06
850	22	42.8	12.3	21.5	6.0	0.868	0.761	3.63	2.15	5.43	3.24
1,000	6	44.5	12.1	24.0	7.2	0.665	0.290	2.87	0.81	4.81	1.63

NOTE. One patient treated at 850 mg had almost identical SN-38G concentrations at 8.5 and 25 hours, resulting in an SN-38G AUC_{0-∞} of 196.56 h · mg/L and a GR of 178.69, which have been removed from the calculations of the means and SDs in the 850-mg-dose group.

Abbreviations: AUC_{0-∞}, area under the concentration-time curve from zero to infinity; CL, clearance rate; GR, glucuronidation ratio; SD, standard deviation.

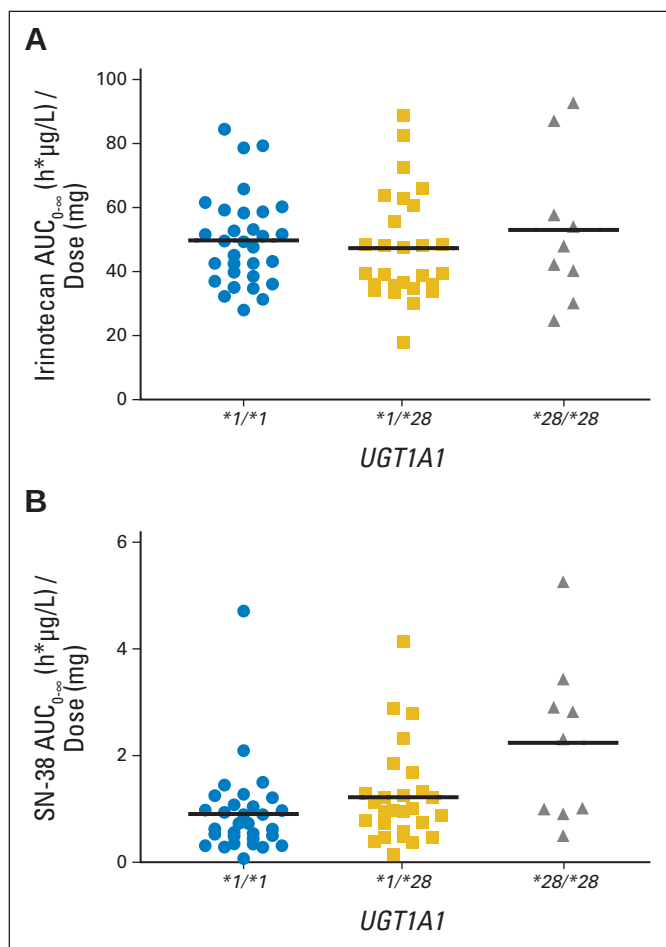


Fig 1. Relationship between the *UGT1A1**28 genotype and dose-adjusted areas under the curve (AUCs) of irinotecan (A; $P = .62$) and SN-38 (B; $P = .01$). Horizontal bars represent the means.

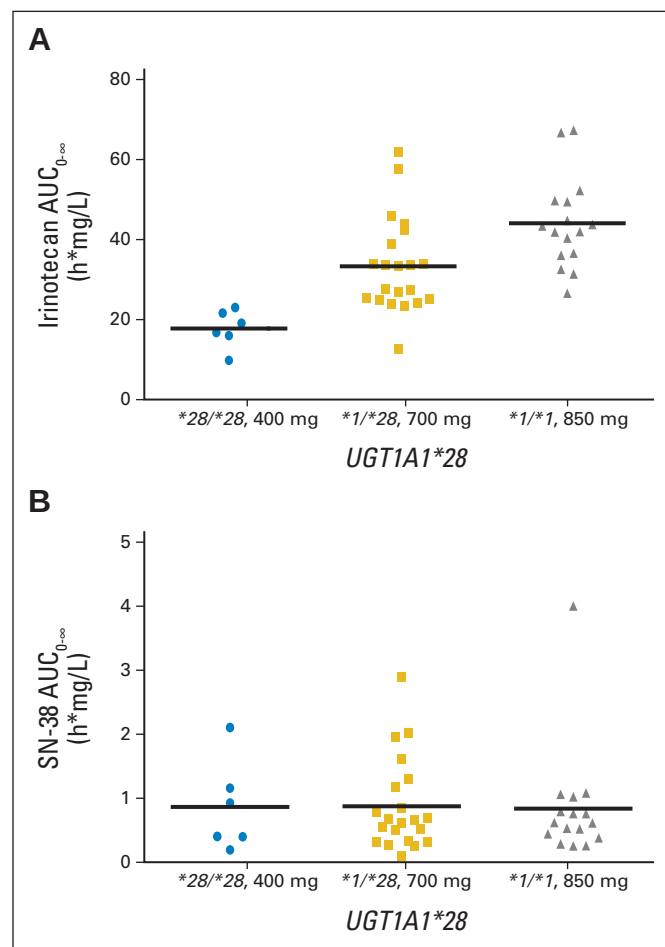


Fig 2. Area under the curve (AUC) of irinotecan (A; $r^2 = 0.39$; $P < .001$) and SN-38 (B; $r^2 = 0.0003$; $P = .97$) at the maximum-tolerated dose (MTD) for each genotype. Horizontal bars represent the means.

genotype could tolerate an even higher dose of 850 mg (470 mg/m^2); only four DLTs were observed among 16 patients treated at this dose level. An irinotecan dose of 500 mg/m^2 has been shown to be tolerable in patients with refractory cancer who have favorable characteristics (eg, good risk, not heavily pretreated),²¹ but *UGT1A1**28 was not used for dose selection in that study. In other *UGT1A1**28 genotype-directed studies of FOLFIRI, patients with the *1/*1 genotype tolerated approximately twice the dose recommended by the label,^{19,22} probably because the therapeutic window is wider in the biweekly regimen of FOLFIRI (standard dose, 180 mg/m^2) than in the regimen administered once every 3 weeks (standard dose, 350 mg/m^2). However, the patient populations are quite different between our study (heavily pretreated, different tumor types) and the FOLFIRI studies (first-line treatment of metastatic colorectal cancer).^{19,22} Similar to this study, these studies with FOLFIRI also showed that the patients with the *1/*28 genotype tolerated a lower dose relative to the patients with the *1/*1 genotype, confirming the importance of individualized dosing by genotype. The *1/*28 genotype confers an intermediate-metabolizer phenotype^{13,23-25} and an intermediate risk of toxicity.⁴

The pharmacokinetics of irinotecan are informative about the relationship among genotype, dosing, and neutropenia. Although irinotecan pharmacokinetics retains its linearity even at higher doses,²⁶

the *UGT1A1**28 status of patients clearly affects the exposure to the active metabolite SN-38, as shown by a linear, direct relationship with the *UGT1A1**28 genotypes (Fig 1). Because this relationship already has been demonstrated in many studies,³⁻⁶ it is important to show that a strategy of individualizing dosing of irinotecan is able to individualize the exposure to SN-38. As shown in Figure 2, although irinotecan AUC increases according to the different MTDs in each genotype group, the mean SN-38 AUC levels are comparable across the different MTDs in each genotype group. This normalization of SN-38 AUC by genotype-directed dosing may be key to preserving antitumor efficacy, even when patients with the *28/*28 genotype are treated at lower doses. BSA, as expected, is not a determinant of the pharmacokinetic variability, and considerations on dosing by mg/m^2 should be made—including a comparison of flat dosing versus BSA dosing at the MTD in additional studies that use genotype-guided dosing of irinotecan.

A single-agent, dose-finding study such as this has pros and cons. Irinotecan is given mostly in combination regimens, and its use as a single agent is limited, although it might have more widespread use as a single agent in countries where expensive biologics are neither reimbursed nor available,^{27,28} because irinotecan is a generic drug. In Asian countries, *UGT1A1**6 should be considered in addition to *UGT1A1**28 to inform dosing of irinotecan.⁶ Single-agent studies have the

advantage of being not confounded by overlapping toxicities, and the pharmacokinetic data are not influenced by potential drug-drug interactions. These single-agent studies demonstrate a proof of concept so that they can be followed by additional genotype-directed trials in the combination setting.

These safety studies represent another important step toward precision medicine in oncology. The dose-escalation studies conducted so far,^{19,22} including ours, clearly show that a significant group of patients treated with irinotecan is probably being under-dosed. However, practice cannot be changed until evidence for improved efficacy of this approach is in fact demonstrated (ie, that increasing dosing by genotype confers higher response and/or longer survival compared with standard dosing). The studies of FOLFIRI in patients treated for first-line metastatic colorectal cancer suggest that higher doses may confer a clinical advantage (measured as time to progression).^{19,22} These are small studies, and efficacy was a secondary end point. In the highly refractory population of patients with solid tumors included in this trial, four partial responses were observed among 48 evaluable patients with diseases known to respond to irinotecan. Although three of them occurred at a higher dose of 850 mg, it is still premature to conclude that higher doses by genotype are more efficacious. A prospective, phase II study in patients with metastatic colorectal cancer treated with FOLFIRI plus bevacizumab in the first-line setting will evaluate the effect of genotype-directed dosing of irinotecan on survival.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

- Meyerhardt JA, Mayer RJ: Systemic therapy for colorectal cancer. *N Engl J Med* 352:476-487, 2005
- Innocenti F, Ratain MJ: Pharmacogenetics of irinotecan: Clinical perspectives on the utility of genotyping. *Pharmacogenomics* 7:1211-1221, 2006
- Ramchandani RP, Wang Y, Booth BP, et al: The role of SN-38 exposure, *UGT1A1**28 polymorphism, and baseline bilirubin level in predicting severe irinotecan toxicity. *J Clin Pharmacol* 47:78-86, 2007
- Innocenti F, Undevia SD, Iyer L, et al: Genetic variants in the UDP-glucuronosyltransferase 1A1 gene predict the risk of severe neutropenia of irinotecan. *J Clin Oncol* 22:1382-1388, 2004
- Minami H, Sai K, Saeki M, et al: Irinotecan pharmacokinetics/pharmacodynamics and *UGT1A* genetic polymorphisms in Japanese: Roles of *UGT1A1**6 and *28. *Pharmacogenet Genomics* 17:497-504, 2007
- Han JY, Lim HS, Shin ES, et al: Comprehensive analysis of *UGT1A* polymorphisms predictive for pharmacokinetics and treatment outcome in patients with non-small-cell lung cancer treated with irinotecan and cisplatin. *J Clin Oncol* 24:2237-2244, 2006
- Toffoli G, Cecchin E, Corona G, et al: The role of *UGT1A1**28 polymorphism in the pharmacodynamics and pharmacokinetics of irinotecan in patients with metastatic colorectal cancer. *J Clin Oncol* 24:3061-3068, 2006
- Hoskins JM, Goldberg RM, Qu P, et al: *UGT1A1**28 genotype and irinotecan-induced neutropenia: Dose matters. *J Natl Cancer Inst* 99:1290-1295, 2007
- Pfizer: Camptosar Package Insert. New York, NY, Pfizer, 2012
- Egorin MJ: Horseshoes, hand grenades, and body-surface area-based dosing: Aiming for a target. *J Clin Oncol* 21:182-183, 2003
- Mathijssen RH, Verweij J, de Jonge MJ, et al: Impact of body-size measures on irinotecan clearance: Alternative dosing recommendations. *J Clin Oncol* 20:81-87, 2002
- Iyer L, Das S, Janisch L, et al: *UGT1A1**28 polymorphism as a determinant of irinotecan disposition and toxicity. *Pharmacogenomics* 3:43-47, 2002
- Iyer L, Hall D, Das S, et al: Phenotype-genotype correlation of in vitro SN-38 (active metabolite of irinotecan) and bilirubin glucuronidation in human liver tissue with *UGT1A1* promoter polymorphism. *Clin Pharmacol Ther* 65:576-582, 1999
- Therasse P, Eisenhauer EA, Verweij J: RECIST revisited: A review of validation studies on tumour assessment. *Eur J Cancer* 42:1031-1039, 2006
- Gillis NK, Patel JN, Innocenti F: Clinical implementation of germ line cancer pharmacogenetic variants during the next-generation sequencing era. *Clin Pharmacol Ther* 95:269-280, 2014
- Cancer Genome Atlas Research Network, Weinstein JN, Collisson EA, et al: The Cancer Genome Atlas Pan-Cancer analysis project. *Nat Genet* 45:1113-1120, 2013
- Sleijfer S, Bogaerts J, Siu LL: Designing transformative clinical trials in the cancer genome era. *J Clin Oncol* 31:1834-1841, 2013
- Innocenti F, Schilsky RL: Translating the cancer genome into clinically useful tools and strategies. *Dis Model Mech* 2:426-429, 2009
- Marcuello E, Páez D, Paré L, et al: A genotype-directed phase I-IV dose-finding study of irinotecan in combination with fluorouracil/leucovorin as first-line treatment in advanced colorectal cancer. *Br J Cancer* 105:53-57, 2011
- Hall D, Ybazeta G, Destro-Bisoli G, et al: Variability at the uridine diphosphate glucuronosyltransferase 1A1 promoter in human populations and primates. *Pharmacogenetics* 9:591-599, 1999
- Merrouche Y, Extra JM, Abigeres D, et al: High dose-intensity of irinotecan administered every 3 weeks in advanced cancer patients: A feasibility study. *J Clin Oncol* 15:1080-1086, 1997
- Toffoli G, Cecchin E, Gasparini G, et al: Genotype-driven phase I study of irinotecan administered in combination with fluorouracil/leucovorin in patients with metastatic colorectal cancer. *J Clin Oncol* 28:866-871, 2010
- Zhang D, Zhang D, Cui D, et al: Characterization of the UDP glucuronosyltransferase activity of human liver microsomes genotyped for the *UGT1A1**28 polymorphism. *Drug Metab Dispos* 35:2270-2280, 2007

24. Ramirez J, Mirkov S, Zhang W, et al: Hepatocyte nuclear factor-1 alpha is associated with *UGT1A1*, *UGT1A9* and *UGT2B7* mRNA expression in human liver. *Pharmacogenomics J* 8:152-161, 2008

25. Innocenti F, Grimsley C, Das S, et al: Haplotype structure of the UDP-glucuronosyltransferase

1A1 promoter in different ethnic groups. *Pharmacogenetics* 12:725-733, 2002

26. Chabot GG, Abigerges D, Catimel G, et al: Population pharmacokinetics and pharmacodynamics of irinotecan (CPT-11) and active metabolite SN-38 during phase I trials. *Ann Oncol* 6:141-151, 1995

27. Kmietowicz Z: Task force hopes to deliver affordable cancer drugs to developing countries. *BMJ* 339:4506b, 2009

28. Farmer P, Frenk J, Knaul FM, et al: Expansion of cancer care and control in countries of low and middle income: A call to action. *Lancet* 376:1186-1193, 2010

GLOSSARY TERMS

UGT1A1 (UDP-glucuronosyltransferase 1A1): an isoform of uridine-diphosphoglucuronate glucuronosyltransferases. UGT1A1 is responsible for the glucuronidation of bilirubin, xenobiotic compounds, and endogenous steroids. Variants of UGT1A1 are known to affect the glucuronidation of SN-38, the active metabolite of irinotecan.

area under the curve (AUC): a measure of the amount of drug in the blood over a set period of time (eg, 24 hours) that can be used to determine drug exposure.

genotype: the specific genetic makeup of a given individual. Although genotypes give rise to the phenotype of an individual, genotypes and phenotypes are not always correlative. For example, some genotypes are expressed only under specific environmental conditions.

irinotecan: a plant alkaloid. A prodrug is converted to a biologically active metabolite 7-ethyl-10-hydroxy-camptothecin (SN-38) by a carboxylesterase-converting enzyme. SN-38 inhibits topoisomerase I activity.

neutropenic fever: an oral temperature of at least 100.4°F for at least 1 hour when the absolute neutrophil count is $< 0.5 \times 10^9/L$.

pharmacokinetics: a branch of pharmacology that studies the relationship between drug exposure level, time course of exposure, and the overall response of an organism. Although pharmacokinetics is largely applied to drugs, it is also applicable to other compounds such as nutrients, toxins, hormones, etc. Pharmacokinetics is subdivided into absorption and disposition (distribution, metabolism, and excretion) and is generally referred to as ADME (absorption, distribution, metabolism, excretion). With respect to drugs administered, all processes occur in tandem once a drug dose is administered. In clinical trials, phase I studies will typically study pharmacokinetics and safety of the drug.

phenotype: the overall appearance of an organism, or the observable expression of a specific trait, determined by its genotype and environmental factors.

prodrug: a drug that is given in an inactive form and is bioactivated to a pharmacologic drug by one or more metabolic processes.

Appendix ROSSI01



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Appendix ROSSI02

WJG 20th Anniversary Special Issues (14): Pancreatic cancer

Therapeutic options for the management of pancreatic cancer

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Abstract

Since its initial characterization, pancreatic ductal adenocarcinoma has remained one of the most devastating and difficult cancers to treat. Pancreatic cancer is the fourth leading cause of death in the United States, resulting in an estimated 38460 deaths annually. With few screening tools available to detect this disease at an early stage, 94% of patients will die within five years of diagnosis. Despite decades of research that have led to a better understanding of the molecular and cellular signaling pathways in pancreatic cancer cells, few effective therapies have been developed to target these pathways. Other treatment options have included more sophisticated pancreatic cancer surgeries and combination therapies. While outcomes have improved modestly for these patients, more effective treatments

are desperately needed. One of the greatest challenges in the future of treating this malignancy will be to develop therapies that target the tumor microenvironment and surrounding pancreatic cancer stem cells in addition to pancreatic cancer cells. Recent advances in targeting pancreatic stellate cells and the stroma have encouraged researchers to shift their focus to the role of desmoplasia in pancreatic cancer pathobiology in the hopes of developing newer-generation therapies. By combining novel agents with current cytotoxic chemotherapies and radiation therapy and personalizing them to each patient based on specific biomarkers, the goal of prolonging a patient's life could be achieved. Here we review the most effective therapies that have been used for the treatment of pancreatic cancer and discuss the future potential of therapeutic options.

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Key words: Pancreatic cancer; Pancreatic cancer stem cells; Microenvironment; Surgical resection; Neoadjuvant therapy; Adjuvant therapy; Chemotherapy; Radiation; Personalized therapy

Core tip: Pancreatic ductal adenocarcinoma has challenged researchers for decades. It remains one of the most deadly cancers due to the complex molecular and genetic makeup of its cancer cells and their surrounding microenvironment. In addition, there are no valid screening tests available to detect pancreatic cancer in its early stages. Yet, as knowledge of this cancer has evolved over time, so have novel methods for treating it. Researchers have a deeper understanding of pancreatic cancer now than ever before. The future holds much promise for new breakthroughs that will significantly improve patient outcomes.

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INTRODUCTION

Despite the improved survival rates noted in numerous cancers, including breast^[1-3], prostate^[4] and colon cancer^[5], the overall survival rates for patients diagnosed with pancreatic cancer have shown little improvement over the past thirty years^[6-8]. Pancreatic ductal adenocarcinoma (PDA) remains one of the most rapidly progressive and deadly malignancies worldwide^[4]. The prevention of pancreatic cancer is difficult to assess, due to limited studies identifying potential risk factors compounded with the multifactorial, heterogeneous nature of the disease. Cigarette smoking has been noted to double the risk of pancreatic cancer, yet only accounts for 20%-25% of the cases^[9,10]. Additionally, family history may also contribute a significant role as 5%-10% of individuals with pancreatic cancer report an incidence of pancreatic cancer in a close family member^[11]. This risk is further substantiated when there is a larger number of family members with pancreatic cancer and a decrease in age of onset in kindred^[12]. Other noted risk factors include alcohol abuse^[13], a high-fat diet^[14,15], and certain trace elements^[16].

The challenge of diagnosing PDA at an early stage further contributes to the dismal five-year survival rate that is projected for patients. Located in the retroperitoneum of patients who present with non-specific symptoms, PDA is not diagnosed until it has reached an advanced clinical stage in 80% of patients^[17]. In addition, lack of effective screening and early biomarker detection methods have prevented clinicians from identifying this cancer in a pre-malignant stage. Ideally, visual evaluation *via* computerized tomography (CT) and magnetic resonance imaging (MRI) should be incorporated upon suspicion of pancreatic cancer for detection and resectability assessment^[18]. Although CT scan has often been utilized to detect pancreatic cancer^[19-21], reliance on MRI, particularly in regard to assessing local invasion and metastasis, has increased^[22]. Other imaging may also provide certain benefits, such as endoscopic ultrasound for investigating vascular invasion^[23], fludeoxyglucose-positron emission tomography scanning for recurrent tumors^[24], and laparoscopy for more accurate staging^[25]. While the use of these techniques remains helpful to determine prognosis and treatment regimen for patients diagnosed with pancreatic cancer, none have been validated as effective screening tests for general or high risk populations.

Once diagnosed, a number of chemotherapy, radiation and combination therapy regimens have been used to treat patients with ductal pancreatic tumors. Unfortunately, the dynamic molecular and cellular makeup of individual pancreatic tumors, renders many of them resistant to the majority of these therapies. Although surgical resection has been shown to increase patient survival

by 10 mo^[26], the majority of patients who undergo these procedures experience comorbidities and recurrence. Current research has identified additional sources of therapeutic resistance in the microenvironment of these tumors. Characterized by stromal proliferation, reduced angiogenesis and a unique subset of cells known as cancer stem cells (CSCs), the tumor microenvironment has become a target of new therapeutic agents.

While improved understanding of pancreatic cancer biology has lead to several therapeutic breakthroughs in the treatment of PDA, major progress toward improving survival rates in patients has been extremely slow. However, as our understanding of this tumor's therapeutic resistant nature improves, so will future progress in treating pancreatic cancer.

CLINICAL PRESENTATION AND DIAGNOSIS

One of the greatest challenges in treating pancreatic ductal adenocarcinoma (PDA) is discovering it in the pre-malignant stage. The average patient diagnosed with pancreatic cancer is in their seventh decade of life and presents to their primary care physician with general symptoms of abdominal pain and weight loss^[27]. Not only is the pancreas difficult to palpate due to its retroperitoneal location, but there are also no specific blood tests to confirm suspicion of malignancy. More specific symptoms, such as unexplained jaundice^[28], onset of diabetes^[29] and development of thromboembolic disease^[30] are more diagnostic of pancreatic cancer, but do not present until later stages of the disease. The primary comorbidities associated with PDA include biliary obstruction, infection, ascites, pancreatic insufficiency and in advanced stages of the disease, cachexia^[31]. Unfortunately, once a patient presents with these symptoms, the disease has often already reached its malignant stage and the patient may never be able to receive treatment.

Effective screening tests to provide early diagnosis of pancreatic cancer could potentially prevent these symptoms. The ones that do exist are not validated. For example, although endoscopic ultrasounds provide a higher yield of detecting pancreatic cancer in its early stages, the comorbidities associated with this procedure render it an unsuitable screening test in the general population. As a result, studies are currently underway to identify high risk individuals who may benefit from this invasive procedure^[32-34]. Other techniques, such as cross-sectional imaging could be used to identify asymptomatic pancreatic neoplasms for surgical resection^[34] as long as they are confirmed by CT or MRI techniques which provide better resolution between normal and neoplastic pancreatic tissue^[35].

Although a greater understanding of the molecular events in pancreatic cancer tumorigenesis has lead to the discovery of biomarkers that help to predict the tumor's response to treatment, there has been no use of these markers in cancer drug development^[36]. The only biomarker

Table 1 Cellular mechanisms of therapeutic resistance in pancreatic cancer

Cellular pathways	Mutated gene	Ref.
Cell-cycle control	CDK2NA (90%); APC2	Almoguera <i>et al</i> ^[54] ; Schutte <i>et al</i> ^[71] ; Hahn <i>et al</i> ^[72]
RAS	KRAS (90%); MAP2K4	Almoguera <i>et al</i> ^[54] ; Hruban <i>et al</i> ^[56] ; Pellegata <i>et al</i> ^[57] ; Hezel <i>et al</i> ^[58] ; Maitra <i>et al</i> ^[59]
DNA damage repair	TP53 (75%-90%)	Almoguera <i>et al</i> ^[54] ; Redston <i>et al</i> ^[67] ; Olive <i>et al</i> ^[68]
TGF-β	DPC4 (50%), SMAD4	Almoguera <i>et al</i> ^[54] ; Yachida <i>et al</i> ^[73]
Apoptosis	CASP10; CAD	Jones <i>et al</i> ^[77]
Cell adhesion	FAT; PCDH9	Jones <i>et al</i> ^[77]
Hedgehog	GLI1; GLI3	Jones <i>et al</i> ^[77]
Integrin	ILK; LAMA1	Jones <i>et al</i> ^[77]
JNK	MAP4K3; TNF	Jones <i>et al</i> ^[77]
Small GTPases	PLCB3; RP1	Jones <i>et al</i> ^[77]
Wnt-β-catenin	MYC; TSC2	Jones <i>et al</i> ^[77]

APC: Adenomatous polyposis coli; CDK2NA: Cyclin-dependent kinase inhibitor 2 A; CAD: Carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase; CASP10: Caspase 10; DPC4: deleted in pancreatic cancer, locus 4; FAT: Fat tumor suppressor; GLI 1: Glioma-associated oncogene; GLI3: Glioma-associated oncogene 3; GTPases: Guanosine triphosphate; Wnt-B-catenin: Wingless type B-catenin; ILK: Integrin-linked kinase; JNK: c-Jun N-terminal kinases; KRAS: Kristen rat sarcoma; LAMA1: Laminin A-1 chain; MAP2K4: Mitogen-activated protein kinase kinase 4; MAP4K3: Mitogen-activated protein-3 kinase-3; TNF: Tumor necrosis factor; MYC: Myelocytomatosis oncogene; PCDH9: Protocadherin 9; PLCB3: Phospholipase C, beta 3; RP1: Retinitis pigmentosa 1; SMAD4: Mothers against decapentaplegic homolog 4; TGF-β: Transforming growth factor β; TP53: Tumor protein 53; TSC2: Tuberous sclerosis 2; RAS: Rat sarcoma.

that has shown a great deal of promise in therapeutic monitoring and in identifying the recurrence of pancreatic cancer after treatment is the carbohydrate antigen 19-9 (CA 19-9), a sialylated Lewis blood group A antigen secreted by many pancreatic lesions^[37]. Yet, CA 19-9 is not specific for pancreatic cancer and therefore cannot be used to screen for this tumor. Several other conditions, including hepatobiliary diseases, pancreatic diseases and gastrointestinal malignancies, bronchitis, congestive heart failure, cystic fibrosis, diverticulitis, lung cancer, ovarian cysts, pleural effusions, renal cysts and rheumatoid arthritis may present with elevated levels of CA 19-9^[38]. In addition, approximately 10% of patients with pancreatic cancer are negative for Lewis antigen a or b. As a result, these patients are unable to synthesize CA 19-9 and will have no detectable levels of this biomarker, even in advanced stages of pancreatic cancer^[39]. Although measurement of serum CA 19-9 levels has clinical significance in determining treatment and prognosis for patients with known pancreatic cancer, its usefulness as a diagnostic screening tool of the disease is not substantiated^[40].

Upon diagnosis of pancreatic cancer, treatment and management of patients should utilize a multidisciplinary team including, primary care physicians, medical oncolo-

gists, radiation oncologists, surgeons, endocrinologists, radiologists and pathologists^[41]. Cancer staging subsequently follows, with the American Joint Committee on Cancer providing the standard model, based upon the tumor-node-metastasis system^[42]. However, not all criteria regarding tumor staging can be measured prior to surgical intervention. As a result, the majority of staging for pancreatic cancer incorporates imaging results and liver function tests. From these results, patients with pancreatic cancer can often be classified into three major cohorts: (1) patients with a resectable tumor or borderline resectable tumor; (2) patients with a locally invasive tumor without metastasis; and (3) patients with a systemically disseminated tumor.

Appropriately designating cases into the proper subgroup is vital to ensure appropriate treatment and management of patients presenting with pancreatic cancer. Often, fine needle aspiration guided by endoscopic ultrasonography is necessary to obtain histological confirmation^[43,44], especially prior to the initiation of chemotherapy and radiation. Throughout the treatment process, CA 19-9 should be continuously measured^[45,46]. Nonetheless, previous studies still support the usefulness of CA 19-9 in predicting patient response to chemotherapy^[47,48], preoperative prognosis^[49], as well as assessing treatment response^[50,51], overall survival^[51-53], and recurrence^[51].

THERAPEUTIC RESISTANCE IN PANCREATIC CANCER

Cellular mechanisms of therapeutic resistance

In an effort to understand the therapeutic resistant (Table 1) nature of PDA, researchers have attempted to characterize the molecular and cellular components of the pancreatic cancer cells as well as the desmoplasia that surrounds them. Although pancreatic cancer displays pathologic and clinical heterogeneity, data suggests the majority of PDA express a successive accumulation of highly penetrant genetic alterations that occur at four genetic loci: K-ras, p53, cdkn2a and smad4/DPC4^[54]. Originating in the ductal epithelium, pancreatic cancer evolves from a premalignant lesion to a highly invasive metastatic disease^[55].

Ninety percent of tumors have point mutations that are specific for the KRAS2 oncogene, resulting in the constitutive production of the Ras protein^[56-59]. Occurring early in tumorigenesis, these point mutations are essential for maintaining the malignant phenotype because once activated, Ras initiates a signal transduction cascade that activates proliferative and cell survival pathways and increases cell invasion^[60,61]. The majority of the point mutations occur on codon 12 of the ras protein and give rise to pancreatic tumor-specific neo-antigens. Several studies demonstrated these antigens are recognized by helper T-cells and cytotoxic T-cells^[62,63]. Using this knowledge, scientists developed personalized peptide vaccines corresponding to the K-ras mutations present in the tumors of patients enrolled in one clinical trial^[64]. The vaccine was

Table 2 Extracellular mechanisms of therapeutic resistance in pancreatic cancer

Potential therapeutic targets	Extracellular response	Ref.
K-ras mutant oncogene	Proliferation of desmoplastic reaction (leukocytes, fibroblasts, endothelial cells, neuronal cells, collagen, hyaluron): upregulation of GM-CSF	Chu <i>et al</i> ^[78] ; Neesse <i>et al</i> ^[79] ; Ying <i>et al</i> ^[81] ; Nolan-Stevaux <i>et al</i> ^[82] ; Bayne <i>et al</i> ^[87]
Sonic hedgehog (SHH)	Growth and differentiation of stromal fibroblasts	Bailey <i>et al</i> ^[83] ; Tian <i>et al</i> ^[84] ; Olive <i>et al</i> ^[85]
Tumor associated macrophages (TAMs); cancer associated fibroblasts (CAFs); regulatory T-cells (Treg); myeloid derived suppressor cells	Evasion of the immune system	Bayne <i>et al</i> ^[87] ; Pylayeva-Gupta <i>et al</i> ^[88]
Desmoplastic reaction	Anti-angiogenesis; hypoxic tumor environment	Komar <i>et al</i> ^[86]

K-ras: Kinase-rat sarcoma; GM-CSF: Granulocyte macrophage colony-stimulating factor.

proven safe and tolerable and resulted in a more efficient immunologic attack on the tumor^[65]. As a result, patients given the vaccine demonstrated a more favorable clinical outcome than those not given the vaccine. Combined with surgical resection, a long-term immune response initiated by the K-ras vaccine has resulted in a 10-year survival in some patients. These results may implicate a role for the K-ras vaccine as an adjuvant treatment option in the future^[66,67].

Rather than being activated like the mutated KRAS2 oncogene, the p53 tumor suppressor gene is inactivated in 75%-90% of pancreatic tumors^[68,69]. As a result, there is an impaired response to DNA damage in pancreatic epithelial cells, impaired apoptosis and impaired cell cycle control^[70,71]. Two other tumor suppressor genes, *p16Ink4a* and *p15ARF* are encoded by the *cdkn2a* locus. Inactivation mutations in these genes are present in about 90% of human PDA^[72,73].

A fourth common mutation seen in more than half of pancreatic cancers causes an alteration in DPC4^[74]. These mutations confer a metastatic phenotype. The genetic makeup of the patient determines the number and combination of these mutations that will be present in their PDA. Patients with three or four mutated genes will have a much worse prognosis than those with one or two. The variable expressivity of these tumors presents a challenge in effectively treating them^[75].

In addition to these four primary genetic alterations in PDA many other less-frequent mutations occur as well^[76-78]. According to a comprehensive genetic analysis of 24 pancreatic cancers, an average of more than 60 genetic abnormalities, primarily point mutations, per tu-

mor were noted in the PDA phenotype. While these mutations have been organized into 12 functional cancer-relevant pathways, not all tumors have alterations in each of these pathways. In addition, key mutations in select pathways appear to differ from one tumor to another^[78]. These pathways may confer therapeutic resistance in the pancreatic tumor. Significant genomic instability in pancreatic cancer may also reduce the effectiveness of therapeutic agents by contributing to acquired chemoresistance.

Extracellular mechanisms of therapeutic resistance

Paracrine signals from pancreatic cancer cells stimulate the extracellular proliferation of leukocytes, fibroblasts, endothelial cells, neuronal cells, collagen and hyaluron (Table 2). This extracellular proliferation of cells is known as a desmoplastic reaction. It forms a thick stromal environment around the pancreatic cancer cells^[79,80]. Studies have demonstrated that the signals that influence the proliferation of the desmoplastic reaction originate from the K-ras mutant oncogene in the epithelium of the pancreatic cancer cells^[81,82].

In addition to the K-ras mutant signaling pathway, there has been an effort by researchers to understand the roles of other signaling pathways between the pancreatic cancer cells and their microenvironment. Sonic hedgehog (SHH) functions similarly to the K-ras mutant. Although it is over expressed in pancreatic cancer cells during the early stages of their development, SHH does not act on the SHH pathway in these cells^[83]. Instead, it acts in a paracrine fashion in the extracellular fibroblasts, resulting in their growth and differentiation^[84,85].

The desmoplastic reaction not only provides a mechanical barrier to the pancreatic cancer cells, but it is also thought to contribute to the anti-angiogenic environment that is characteristic of pancreatic ductal adenocarcinoma. Both properties directly affect therapeutic efficacy. Inadequate drug delivery to the site of the tumor is directly correlated with a negative patient outcome^[86].

Researchers have also suggested a role for the tumor stroma in the T-lymphocyte depleted microenvironment of the PDA. Several cell types found in the desmoplastic reaction have been associated with tumor associated macrophages, cancer associated fibroblasts, regulatory T-cells and myeloid derived suppressor cells. In addition, a role for a K-ras dependent signaling molecule has been shown to up-regulate granulocyte-macrophage colony stimulating factor when activated. This cytokine promotes the maturation of immature myeloid progenitor cells into myeloid derived suppressor cells^[87,88].

TREATMENT OF PANCREATIC CANCER

Surgical resection

Although surgical resection offers hope for curative therapy, only 20% of patients present with potentially resectable tumors^[89,90]. It is important to note that surgical resection is only considered in patients with completely

Table 3 Therapies for the management of pancreatic cancer

Therapeutic option	Subset	Ref.
Surgical resection	Cephalic pancreatoduodenectomy	Hidalgo ^[41]
	Distal pancreatectomy	
	Total pancreatectomy	
Chemotherapy	Neoadjuvant	Lemmens <i>et al</i> ^[101] ; Gillen <i>et al</i> ^[102] ;
	Gemcitabine	
	Adjuvant	Neoptolemos <i>et al</i> ^[108] ; Burris <i>et al</i> ^[118] ;
	Gemcitabine	
	5-Fluorouracil	Heinemann <i>et al</i> ^[119] ;
	Advanced disease	Reni <i>et al</i> ^[120] ;
	Gemcitabine	Moore <i>et al</i> ^[122] ;
	Gemcitabine + fluoropyrimidines	Neesse <i>et al</i> ^[79]
	Gemcitabine + platinum analogs	
	Gemcitabine + erlotinib	
	FOLFIRINOX	
	Nab-paclitaxel	
Radiation therapy	Neoadjuvant	Pisters <i>et al</i> ^[131] ; Hong <i>et al</i> ^[133] ;
	Radiation + 5-fluorouracil	
	Radiation + paclitaxel	Yeo <i>et al</i> ^[140] ;
	Proton beam radiation + capecitabine	Regine <i>et al</i> ^[138] ;
	Adjuvant	Neoptolemos <i>et al</i> ^[137] ;
	Radiation + 5-Fluorouracil	Moertel <i>et al</i> ^[144] ;
	Radiation + gemcitabine	Schellenberg <i>et al</i> ^[147]
	Radiation + chemotherapy	
	Advanced	
	Radiation + 5-fluorouracil	
	Radiation + chemotherapy	
	Stereotactic body radiotherapy	
Personalized therapy	Target specific point mutations	Jones <i>et al</i> ^[77] ;
	Mitomycin C	Villarroel <i>et al</i> ^[153] ;
	Immune system stimulation	Yanagimoto <i>et al</i> ^[154]

resectable or borderline-resectable tumors (Table 3). Depending on the size and location of the tumor, three operative procedures are potentially utilized, as noted by Hidalgo^[41], with additional removal of adjacent lymph nodes: (1) cephalic pancreatoduodenectomy (whipple procedure); (2) distal pancreatectomy; and (3) total pancreatectomy.

Although additional palliative care is often utilized, controversy surrounds the potential benefits. For example, almost 80% of patients presenting with tumors in the pancreatic head exhibit jaundice due to biliary obstruction^[91,92]. However, previous investigations have conflicting results regarding preoperative biliary drainage with certain studies reporting a decrease in perioperative morbidity and mortality^[93] while others concluding recognizable benefit^[94,95].

Preoperative biliary stenting doubled between 1992 and 2007 due to evidence demonstrating a higher risk of postoperative complications in patients presenting with a tumor in the head of the pancreas. Biliary drainage was further supported by evidence demonstrating its ability to improve liver function, nutritional status and cell-mediated immune function^[93]. Despite intentions to reduce post-operative morbidity and mortality by improving liver function, extensive clinical studies have demonstrated preoperative biliary stenting prolongs time to operation, increases preoperative infection and is associated with overall increased complication rates after surgical proce-

dures^[94,95]. As a result, most studies have advised against routinely performing preoperative biliary drainage and have recommended that patients presenting with jaundice due to a resectable and non-metastatic tumor in the head of the pancreas should undergo early surgery without preoperative biliary resection^[95]. Currently, the only indications for preoperative biliary decompression are for patients who present with severe jaundice, are undergoing neoadjuvant therapy, or have had their surgery postponed due to logistics^[94,95].

Several poor predictors for successful resection have been identified, including lymph node involvement^[96], high tumor grade^[97], large tumor size^[98], elevated CA 19-9 levels^[46], and positive margins of tumor following resection^[41]. These same factors also contribute to recurrence of pancreatic tumors. Even with surgical resection, 5-year survival rates remain dismal, at approximately 20% following surgery^[90]. However, perioperative complications and mortality have significantly decreased over the past decade, likely due to greater hospital clinical volume through centralization^[99,100].

Chemotherapy

Neoadjuvant therapy: Certain patients might receive neoadjuvant therapy, especially if the tumor presents with borderline resectability. In a study utilizing gemcitabine-based chemotherapy, improved tumor resection with increased survival rates was noted in border-line resect-

able cases^[101,102]. However, these effects may only occur in select tumors, with influences by both the genetic composition and microenvironment of the pancreatic cancer^[103,104]. For example, White *et al.*^[105] noted p53 mutations were more common in patients with large residual tumors following treatment with chemoradiation. Moreover, outcomes for neoadjuvant therapy prior to surgically-resectable tumors did not differ when chemotherapy was provided post-operatively^[106]. Chemotherapy with radiation has also been shown to improve survival, but not stage, of cases presenting with locally invasive tumors without metastasis^[107]. However, previous studies do note that surgical interventions are more challenging and increased postoperative stay is associated with patients undergoing resection after neoadjuvant chemoradiation therapy for locally invasive cancer^[106]. Since metastatic pancreatic cancer cannot be completely resected, surgical options are unavailable and hence no neoadjuvant therapy can be provided. Lastly, it is important to note that prior to initiating neoadjuvant therapy, histological confirmation of pancreatic adenocarcinoma is required, unlike surgical resection, which often relies solely on imaging.

Adjuvant chemotherapy: Even following complete, successful resection of pancreatic tumors, overall survival and prognosis remains discouraging. Hence, postoperative chemotherapy or chemoradiation is almost always incorporated in the therapeutic regimen. Postoperative chemotherapy often utilizes gemcitabine or 5-fluorouracil (with concurrent leucovorin as a rescue agent). Both drugs have demonstrated significant increases in patient survival, regardless of initial case presentation. These drugs may also be given simultaneously, however, significant toxicity (especially gastrointestinal) has been reported. Although gemcitabine has often been considered the standard, previous studies do differ on which agents are associated with the most optimal benefits. In a phase III, randomized control trial, Neoptolemos *et al.*^[108] noted no significance difference in survivorship between gemcitabine and 5-fluorouracil (with folinic acid) in patients with resected tumors. In a separate study published in JAMA, the authors concluded that gemcitabine alone should be favored over 5-fluorouracil with leucovorin due to its decreased toxicity^[108].

Developments of other complementary agents to enhance chemotherapeutic effects are currently under review. For example, possible inhibition of Hedgehog signaling^[84] or concurrent use of Smac mimetics^[109], microRNAs^[110], Resveratrol^[111], capecitabine^[112], thymoquinone^[113] or heat-shock protein complements^[114] may promote tumor uptake and damage of administered drugs, such as Gemcitabine administered with concurrent curcumin may also be a potential option, especially in tumors exhibiting gemcitabine-resistance^[115]. In addition to utilizing CA 19-9 and imaging to monitor patient response to chemotherapy, other markers, such as human equilibrative nucleoside transporter 1 levels have also shown to be useful^[116]. Other gene expression levels, as noted in Fujita

et al.^[117], may also be predictive of treatment efficacy, particularly with gemcitabine. Further investigation is required as to whether adjuvant chemotherapy should be administered if prior neoadjuvant therapy before surgery had already been provided.

Chemotherapy for advanced disease: Due to its poor detection rate, 60%-70% of patients present with metastatic pancreatic cancer upon initial diagnosis. In the advanced stage of disease, pancreatic cancer causes imminent mortality for the majority of affected patients and median survival rate is typically 6-8 mo. Therefore, treatment of patients with metastatic pancreatic adenocarcinoma incorporates chemotherapy, targeted-therapy, comorbid conditions, intensive supportive treatment and psychosocial support.

Gemcitabine is currently considered the chemotherapeutic standard of care in treatment of advanced pancreatic cancer^[118]. It has been shown to prolong the average survival rate by 4 mo. In an attempt to improve survival rates, several phase II and phase III trials combined Gemcitabine with fluoropyrimidines and platinum analogs. Most of these combinations failed to show statistically significant survival benefit, however compared to Gemcitabine alone^[119]. In another attempt to prolong patient survival, scientists have developed several Gemcitabine-based polychemotherapy regimens involving 3-4 cytotoxic agents. When Reni *et al.*^[120] performed a randomized trial to test the cisplatin, epirubicin, fluorouracil and gemcitabine (PEFG-regimen) against gemcitabine alone, those patients treated with the PEFEG saw a significant decrease in cancer progression, when compared to those treated with gemcitabine alone^[120]. Yet in regards to survival, the infusional 5-FU/folinic acid, irinotecan, and oxaliplatin (FOLFIRINOX) regimen has been shown to be superior to the PEFEG-regimen.

According to Conroy *et al.*^[121], FOLFIRINOX is the new standard in the treatment of advanced stage pancreatic cancer. Compared to gemcitabine alone, FOLFIRINOX demonstrated a better objective response rate, progression-free survival, overall survival and one-year survival. While the toxicity levels associated with FOLFIRINOX are greater than those caused by gemcitabine, the effects did not seem to have a significant impact on quality of life. In addition, few toxic deaths have been reported.

Inhibitors of epidermal growth factor receptor (EGFR) have also been tested for treatment of metastatic pancreatic cancer. Cetuximab, an anti-EGFR directed antibody and erlotinib, an oral EGFR tyrosine kinase inhibitor have been tested in several randomized trials. However, Moore *et al.*^[122] demonstrated that combining gemcitabine with erlotinib is the only targeted-therapeutic agent that has clinical efficacy. Compared with gemcitabine alone, gemcitabine plus erlotinib showed significant decrease in tumor progression and concurrently increased overall survival rates.

Other targeted therapies have focused on targeting

the desmoplastic stroma, one of the key components of pancreatic cancer that may contribute to impaired drug delivery and thus chemotherapy resistance^[79]. Nab-paclitaxel is one therapy that has been developed to diminish this stromal tissue network. Studies have demonstrated that albumin interacts with secreted protein acidic and rich in cysteine (SPARC), a matrix glycoprotein that has a role in tumor invasion, facilitating the uptake of paclitaxel by the tumor^[123]. Infante *et al.*^[124] have demonstrated that overexpression of SPARC in peritumoral fibroblasts was a negative prognostic indicator in patients with advanced pancreatic cancer^[124]. In a phase I / II trial, Von Hoff *et al.*^[125] demonstrated the ability of nab-paclitaxel to increase median survival rate in patients with metastatic pancreatic cancer.

Similar to the mechanism of action of nab-paclitaxel, new therapies are being developed that target the peritumoral stroma in order to increase tumor perfusion. One such preclinical strategy inhibits the hedgehog signaling pathway, depleting the stroma and increasing angiogenesis to improve delivery of chemotherapeutic agents to the tumor^[126].

Phase II clinical trials have demonstrated a benefit of second-line treatment for patients who are resistant to gemcitabine treatment^[127]. Second-line treatments typically consist of fluoropyrimidines in combination with oxaliplatin^[128]. Limited data exists on how to treat patients who do not tolerate FOLFIRINOX as a first-line therapy. However, Conroy *et al.*^[121] have demonstrated the benefit of using gemcitabine-based therapies in these instances.

The primary prognostic indicators for patient survival are both patient and tumor related. Based on the genetic and morphologic heterogeneity that exists within each individual pancreatic tumor, therapy, dose and length of therapy administration will need to be customized for each Individual patient to ensure optimal treatment.

Radiation

Neoadjuvant radiation therapy: Many studies have demonstrated the important roles for chemotherapy and radiation therapy in preventing the recurrence and improving the resectability of pancreatic tumors. While surgery is currently the only potential curative treatment modality for pancreatic cancer, more than 80% of patients who undergo surgical resection will experience tumor recurrence within 12 mo of their procedure^[129]. Therefore, a great deal of focus has not only been placed on developing effective neoadjuvant and adjuvant therapies, but also on effective preoperative staging techniques to determine candidates who will benefit most from surgical resection^[130]. Since surgery is associated with high rates of morbidity and mortality, many patients do not begin adjuvant therapy until after they have recovered. As a result, there is a long delay before they receive adjuvant therapy. In order to begin more potent treatments earlier and to potentially shrink the tumor before surgery, researchers developed neoadjuvant therapeutic regimens.

Multiple trials of 5-fluorouracil-based chemoradia-

tion have been done to date. At the conclusion of these studies, researchers determined that a combined treatment modality with preoperative rapid-fractionation chemoradiation, Whipple procedure, and intra-operative radiation therapy resulted in minimal toxicity and a small recurrence rate^[131]. In a follow-up study, paclitaxel replaced 5-fluorouracil and was used to treat 35 patients who presented with resectable pancreatic tumors^[132]. Based on the results of this study, researchers concluded that preoperative paclitaxel-based chemotherapy with rapid-fractionation chemoradiation, Whipple procedure and intraoperative radiation therapy resulted in similar outcomes as the previous study, but toxicity levels were greater than those from 5-fluorouracil. In another study, researchers treated patients who presented with tumors in the head of the pancreas with a neoadjuvant chemoradiation regimen of capecitabine with proton beam radiation^[133]. No dose limiting toxicities were observed and the authors concluded that this form of neoadjuvant therapy was feasible. In several other prospective neoadjuvant chemoradiation trials in patients with resectable pancreatic cancers, the rate of resection was high in all studies, ranging from 87%-100%^[107,134,135].

Adjuvant radiation therapy: The median survival rate of patients who undergo surgical resection of a pancreatic tumor is 15-22 mo. Only 20% of patients survive for five years following surgery^[136]. The most common site for pancreatic cancer recurrence is the retroperitoneum. Therefore, adjuvant therapy is needed to improve patient prognosis. In the United States, adjuvant therapy is currently delivered in the form of chemotherapy, chemoradiotherapy or chemotherapy followed by chemoradiotherapy. Standard adjuvant treatment in Europe is chemotherapy alone. These guidelines were based on previous randomized trials that showed improved survival in patients given adjuvant therapy following surgical resection.

The first prospective trial for adjuvant chemoradiotherapy was conducted by the Gastrointestinal Tumor Study Group in 1985. The trial enrolled patients with resectable pancreatic cancer. The protocol called for external beam radiation delivered with 5-fluorouracil. The patients were then given a maintenance dose of 5-fluorouracil for an additional two years following initial treatment. Patients treated with adjuvant chemoradiation achieved a longer median and 2-year survival rate than those not treated with adjuvant therapy. As a result, adjuvant chemoradiation became the most frequently used adjuvant treatment for resectable pancreatic cancer in the United States.

To further assess adjuvant radiation therapy for resectable pancreatic cancer, the European Study Group for Pancreatic Cancer (ESPAC-1) conducted the largest randomized trial to date in 2004^[137]. In order to evaluate the effects of chemoradiotherapy and chemotherapy on patient survival following surgical resection, patients with resectable pancreatic ductal adenocarcinoma were divided into one of four groups: chemotherapy alone;

chemoradiotherapy alone; chemoradiotherapy followed by chemotherapy; or no further treatment. Patients who received chemotherapy followed by chemoradiotherapy had a 5-year survival rate that was 10% less than those who received chemotherapy alone. In addition, patients who received chemotherapy treatment showed a 5-year survival benefit when compared to those who received no chemotherapy. As a result of these findings, the standard of adjuvant treatment in Europe shifted towards chemotherapy only, abandoning postoperative chemoradiation.

A phase III trial was conducted by the Radiation Oncology Group and GI Intergroup around the same time as the ESPAC-1 trial^[138]. This trial compared the 5-fluorouracil-based chemoradiation to gemcitabine-based chemoradiation. Patients receiving gemcitabine-based chemoradiation had a median survival of 20.6 mo, 3.5 mo more than those given 5-fluorouracil-based chemotherapy. The Charite Onkologie Clinical Studies in GI Cancer 001 (CONKO-001) trial in Germany and Austria showed similar median survival in patients given gemcitabine-based chemotherapy alone^[139].

Additionally, reports from several institutions, including the Mayo Clinic, Johns Hopkins Medical Center and Virginia Mason University have all reported the benefit of adjuvant chemoradiation therapy following resectable pancreatic cancer compared to those who received surgery alone^[140-142].

Management of locally advanced pancreatic cancer:

Patients with locally advanced pancreatic cancer achieve little benefit from surgical resection because their cancer meets the criteria for unresectable cancer: (1) distant metastasis and/or pancreatic lymph node involvement; (2) encasement or occlusion of the superior mesenteric vein or superior mesenteric vein/portal vein confluence; and/or (3) direct involvement of the celiac axis, aorta, inferior vena cava, or superior mesenteric artery^[143]. As a result, chemoradiation is recommended for these patients based on data from several studies.

A 1981 trial conducted by the Gastrointestinal Tumor Study Group compared the effects of high-dose radiation therapy alone; moderate dose radiation combined with 5-fluorouracil and high dose radiation combined with 5-fluorouracil in 194 patients with locally advanced pancreatic cancer. Researchers found that patients administered 5-fluorouracil in combination with low or high dose radiation showed a greater median survival than those treated with radiation alone^[144]. In a follow-up study, the same group demonstrated that chemotherapy, when combined with radiotherapy afforded patients with locally advanced pancreatic cancer a greater median survival when compared to combination chemotherapy alone^[145]. These results were verified by the ECOG trial as well, which demonstrated an increased median survival rate in patients treated with gemcitabine and radiotherapy together as opposed to those treated with gemcitabine alone^[146].

Although chemoradiation has been shown to provide

an increased median survival in patients with locally advanced pancreatic cancer by 9-13 mo, many of these patients progress to the metastatic stage of disease shortly after therapy. Perhaps a better approach to these patients would be to begin a chemotherapy regimen, restage their cancer after completion of initial treatment, and follow up with chemoradiation in patients who do not demonstrate metastatic disease progression. Radiation in these patients could relieve pain associated with disease by slowing local progression.

Stereotactic body radiotherapy: An evolving radiation therapy for treatment of locally advanced pancreatic cancer is stereotactic body radiation therapy. This newer technique uses image guidance to deliver toxic radiation doses directly to tumors. As a result, there is less systemic involvement, and patient outcomes are improved without having to undergo daily treatments. However, the major challenge of this novel therapy is accurately characterizing the tumor in terms of size, number and location. In order to do so, precise diagnostic tests and real-time imaging techniques are used. In addition, each treatment regimen is tailored to each individual patient. To date, scientific literature suggests stereotactic body radiotherapy does slow local progression in patients with locally advanced pancreatic cancer^[147-149]. However, it does not increase overall survival rate because patient mortality is due to distant metastases.

Advances in radiation therapy techniques: Over the past decade, major advances in radiation therapy have been in treatment planning and more precise delivery methodologies. One technique, intensity-modulated radiotherapy, decreases systemic toxicities in patients by modifying radiation dose delivery specifically to the tumor sites, sparing surrounding normal tissue^[150,151]. Another technique, image-guided radiotherapy, has provided more accurate visualization and real-time tracking of viscera-located tumors and thus has enabled more precise delivery of high-dose therapeutic beams of radiation to these tumors and prevented adverse effects in normal tissue^[152].

In order to improve patient outcome and prolong median survival rate, additional studies are needed to define the optimal role of adjuvant and neoadjuvant treatment in patients with resectable pancreatic cancer. As radiation therapies become more precise and customized to individual patients, it will be necessary to continue to investigate their future role in the treatment of pancreatic adenocarcinoma, especially as a greater understanding of the molecular pathways involved in the carcinogenesis and progression of this disease are understood.

Personalized therapy: In an article published in *Science*, Jones *et al.*^[77] performed a comprehensive genome assessment on 24 different pancreatic cancers. Results revealed an average of 63 genetic mutations per cancer, spanning 12 separate signal transduction pathways. This study sup-

ports the notion of pancreatic cancer being a genetically heterogeneous malignancy, partially accounting for its notable resistance to therapy as well as varied responses to treatment. Moreover, this finding likely explains why no candidate gene has been identified in the treatment of pancreatic cancer. This heterogeneity will likely dictate an individualized, unique approach for each particular case, which has already shown to be effective against even advanced pancreatic cancer stages. In one such case report, Villarroel *et al*^[153] identified Mitomycin C, a DNA-damaging agent, as a highly effective agent by utilizing a xenograft derived from the patient's tumor. Upon administration of this drug, the patient exhibited notable clinical benefits for over three years, despite the tumor previously being gemcitabine resistant. Personalized immune system stimulation may also be a viable option in treatment of unresectable disease. For example, Yanagimoto *et al*^[154] incorporated a vaccine containing individualized, reactive peptides with concurrent gemcitabine treatment, noting a significant correlation between immune boosting and survivorship.

Due to the ongoing advances in DNA sequencing, personalized genomic therapy appears more plausible. Moreover, as scientists continue to identify regions of the genome with high potential for tumor-pathogenesis, this method will only become more efficient. Upon identification, cases can be distributed into cohorts based upon their tumor's genetic composition and administered treatment previously demonstrated to be effective in that particular subgroup. This method would not only identify pertinent biomolecules in pancreatic pathogenesis, but also lead to tumor-specific treatment, which is likely necessary if we are to see any significant improvement in the prognosis of pancreatic cancer.

FUTURE PERSPECTIVES

Despite decades of effort by the scientific community to design sophisticated chemotherapeutic and radiation techniques to combat pancreatic ductal adenocarcinoma, less than 5% of patients with this disease have a 5-year survival rate. The majority of patients have a median survival period of 4-6 mo^[155,156]. A combination of factors including few early symptoms, few accurate biomarkers for early detection, rapid metastasis to the lymphatic system and distant organs, and few effective treatment options, makes this disease one of the most deadly cancers today^[157,158]. Although current therapeutic agents have had limited effects on patient care, there has been substantial advancement in the understanding of the molecular and biological makeup of pancreatic adenocarcinoma. This knowledge has the potential to lead to the development of novel therapies that could significantly improve the lifespan of individuals suffering with this disease.

Such advances in understanding this complex disease have been achieved with genetically-engineered mouse models and patient-derived xenografts. These studies have demonstrated the genetic diversity of pancreatic

ductal adenocarcinoma results from successive accumulation of mutations in several primary oncogenes and tumor suppressor genes, leading to its heterogeneity, instability and early tumor metastasis^[77]. Pancreatic ductal adenocarcinoma is composed of several compartments. In addition to a mature cancer cell population, some researchers have characterized cancer cells that display stem cell properties and are resistant to chemotherapy and radiation therapy, potentiating their ability to metastasize^[56]. Another area of interest is the dense tumor microenvironment that surrounds the pancreatic cancer cells. Composed of collagen I, activated fibroblasts, and inflammatory cells, it has been shown to interact with pancreatic cancer cells in order to foster tumor development, act as a barrier to optimal drug delivery and aid the tumor in invasion and metastasis^[59]. Furthermore, this dense stroma creates a hypoxic microenvironment that pancreatic cancer cells thrive in^[159]. However, the mechanisms by which these cancer cells adapt to these conditions are currently being identified and may serve as additional therapeutic targets in the near future.

Pancreatic cancer cells

Pancreatic ductal adenocarcinoma most likely originates in the ductal epithelium of pancreatic cells^[160]. Neoplastic cells contain one or more of four primary genetic mutations that will ultimately give rise to the invasive form of this disease. Ninety percent of these tumors have mutations in the KRAS2 oncogene, resulting in the activation of proliferative survival signaling pathways. Ninety-five percent have a mutation in the CDKN2A tumor suppressor gene, resulting in the loss of the p16 protein and thus loss of regulation of the G1-S transition of the cell cycle. An abnormal TP53 gene has been identified in 50%-75% of characterized cancer cells, allowing cells to avoid DNA damage control checkpoints and subsequently, apoptotic signals. Another 50% have a deleted SMAD4/MADH4 gene, resulting in aberrant signaling by the TGF- β cell surface receptor^[153].

One study performed genetic analysis on 24 pancreatic ductal adenocarcinomas and reported that each tumor has an average of 63 clinically relevant genetic abnormalities. While these abnormalities differ from one cancer to another, they all seem to play a role in 12 functional cancer-related pathways^[161]. Recently, two studies compared the genetic makeup of distant metastases to their primary metastatic lesions. They found that over time, the distant metastases accumulated additional mutations to those present in the clonal cells from which they arose, adding to the complexity this disease^[162]. Such genetic diversity not only results in different prognoses for patients, but also causes individual tumors to respond differently to common therapeutic agents used in treating pancreatic ductal adenocarcinoma^[163].

The varying degrees of genetic instability that exist between individual pancreatic ductal adenocarcinomas present a greater need for genomic sequencing of individual tumors, followed by personalized therapies to target spe-

cific genes and pathways that have been altered^[164]. Several clinical trials have begun exploring this idea^[165]. In order to incorporate this treatment modality into the clinical setting, several criteria must be met: (1) a high quality tumor tissue sample must be attained at the time of diagnosis; (2) sophisticated bioinformatic analysis of the data must be performed to identify the most relevant mutations in each tissue sample; and (3) model systems must be designed to experimentally test varying treatment options to determine the most effective one for the patient. Perhaps the greatest challenge lies in developing a drug once specific genetic abnormalities have been identified.

Pancreatic cancer stem cells

Recently, investigators have characterized pancreatic cancer cells with stem cell properties^[162]. Known as pancreatic cancer stem cells, these cells have the ability to regrow new tumors when placed into naïve mouse models and are able to maintain long-term tumorigenic potential^[163]. Studies have shown that pancreatic CSCs are not only capable of self renewal, but may also confer therapeutic resistance, and play a role in tumor formation and disease progression^[164,165]. In addition, different cancer stem cell populations perform different biological functions. One of the most recent findings has demonstrated that these cells may transition between epithelial and mesenchymal states, contributing to their highly metastatic potential^[165]. Therefore, eliminating or inhibiting these CSCs with new therapeutic designs could significantly improve patient outcomes. Current therapies have already been designed to target cancer stem cell-specific antigens in order to inhibit their roles in cell survival, adhesion, self renewal and differentiation. A greater understanding of individual CSC populations and how they interact with one another will enable further progress in the treatment of pancreatic cancer^[164,165].

Therapeutic targets of pancreatic ductal adenocarcinoma cancer stem cells include genes located in developmental pathways such as hedgehog, Wnt, Notch, CXCR4 and Met. In addition, targeting apoptotic pathways such as DR5 and nodal-activin could have a significant therapeutic implications. Several preclinical trials have been conducted to target these pathways in models of human pancreatic ductal adenocarcinoma cancer stem cells. By inhibiting these pathways, investigators were able to confer longer-term tumor control when compared to current standard chemotherapeutic regimens, in which tumor regression was significantly shorter-lived. In one recent trial, salinomycin was shown to induce cell death in epithelial-mesenchymal transition-induced cancer stem cells^[124].

Due to the heterogeneity of the cancer stem cell population, future drugs designed to target pancreatic ductal adenocarcinoma stem cells may require clinical trials in which therapies are designed specifically for pancreatic tumors in each individual patient. These customized therapies could potentially serve as adjuvant treatment options for patients following pancreatic tumor resection. Similar to previous clinical trial designs, adjuvant thera-

pies targeting cancer stem cells could be given to patients with or without current conventional chemotherapy and/or chemoradiation to determine which option confers the greatest overall survival rate in patients following surgical resection.

Tumor microenvironment

One of the primary characteristics of pancreatic ductal adenocarcinoma is the dense stroma surrounding the pancreatic cancer cells. Composed of fibroblasts, collagen I and other fibrillar elements, this desmoplastic reaction has become a primary target of current drug therapies^[125]. The key players in the formation and turnover of this dense stroma are pancreatic stellate cells. Certain growth factors [TGF- β 1, platelet-derived growth factor (PDGF) and fibroblast growth factor] activate these cells to myofibroblasts. Not only do these activated myofibroblasts secrete components of the extracellular matrix, but they are also responsible for the poor vascularization of the pancreatic tumor^[166,167]. In addition to forming a mechanical barrier around the pancreatic cancer cells, the stroma has an important role in tumor formation, progression, invasion and metastasis^[168]. Many proteins expressed by stromal cells have been directly correlated with poor prognosis and resistance to current therapies [Cox-2, PDGF receptor, VEGF, stromal-derived factor, chemokines, integrins, secreted protein acidic and rich in cysteine (SPARC), and hedgehog elements].

Pre-clinical models have demonstrated that targeting these receptors and enzymes is associated with antitumor effects. Perhaps one of the most promising targets to date is the hedgehog signaling pathway. Some studies have demonstrated that targeting smoothened resulted in a depletion of the stroma and thereby increased delivery of gemcitabine to the tumor cells^[169]. Another target for therapeutic trials has been SPARC (osteonectin) and hyaluronic acid. SPARC is an extracellular matrix protein that plays a role in collagen turnover in the dense stroma. It is associated with invasion and metastasis in pancreatic ductal adenocarcinoma, and thus poor prognosis in patients with elevated levels^[170]. As mentioned previously, SPARC is the target of the albumin-bound chemotherapy agent, nab-paclitaxel. Phase I / II clinical trials have shown that administration of this drug breaks down the stroma and improves delivery of the chemotherapeutic agent to the site of the tumor^[171]. In addition, in a mouse model of pancreatic ductal adenocarcinoma, investigators demonstrated that administration of pegylated hyaluronidase eliminated hyaluronic acid content, thereby relieving pressure on the blood vessels surrounding the tumor and allowed for increased perfusion of the chemotherapeutic agent to the site of the tumor^[172].

The immunosuppressive nature of the tumor microenvironment has been another stromal characteristic targeted by recent therapeutic development. Using a CD40 antibody combined with gemcitabine chemotherapy, researchers have attempted to reverse immune suppression and drive antitumor T-cell responses in patients with non-resectable pancreatic ductal adenocarcinoma. Studies

have shown that this agent results in tumor regression by stimulating tumor macrophages to attack and deplete the pancreatic cancer stroma^[173].

To date, targeting pancreatic ductal adenocarcinoma has proved most effective when treating patients with locally advanced disease, especially patients with tumors characterized by wild-type DPC4. These tumors are known to be less prone to metastasis and possess higher stromal content. Other tumors, especially those in late stages of the disease, characterized by distant metastases, have not been effectively treated with current stromal-targeting therapeutic agents. This is due to the fact that although pancreatic ductal adenocarcinoma has a rich and hypovascularized stroma, metastases arising from this cancer do not and are not different from other tumors. Therefore, patients who may benefit most from treatment with agents targeting the dense stroma microenvironment would be those with resectable tumors that have not progressed to the advanced stages of disease^[174].

Metabolic pathways

Another conventional way to target pancreatic ductal adenocarcinoma would be to inhibit its major metabolic pathways. In order to do so, researchers would need to prevent its supply of glucose and glutamine; interrupt the pathways that enable it to exist in a hypoxic environment^[175]; and prevent its ability to digest intracellular organelles for energy^[176].

Investigators have identified several key metabolic enzymes to target [hexokinase, pyruvate kinase, lactate dehydrogenase A (LDHA) and ampicillin-activated protein kinase (AMPK)]. Several preclinical trials have demonstrated the anti-tumor effects of agents directed against these enzymes. One study demonstrated a potential clinical application for the LDHA inhibitor, FX11. By blocking the conversion of lactate to pyruvate in cells with p53 mutations, FX11 has antitumor potential. However, to date, there are only two therapies that have shown potential for targeting pancreatic ductal adenocarcinoma metabolism. One of these medications, metformin, is an activator of AMPK. It has been shown to decrease the potential for patients with diabetes to develop pancreatic cancer and to increase survival in diabetic patients with this disease^[177,178]. The other drug used to target the metabolic pathways of is rapamycin. An inhibitor of mTOR, rapamycin has been shown to decrease glucose uptake by reducing levels of Glut1 in pancreatic cancer^[179,180].

In order to inhibit autophagy, a significant mechanism for pancreatic cancer cell survival, investigators have used chloroquine, the antimalarial drug^[181]. In preclinical trials with both allografts and xenografts, chloroquine has been shown to decrease tumorigenesis in a transgenic model and is currently being tested in clinical trials.

CONCLUSION

A greater understanding of the molecular and cellular makeup of pancreatic cancer over the past four decades

has resulted in innovative therapeutic designs to target this aggressive malignancy. We now know that pancreatic cancer is a dynamic, heterogenous and genetically unstable tumor that results from successive mutations early in disease and gives rise to metastases that continue to garner mutations as they travel to distant locations. An equally important understanding of the role the peritumor microenvironment, composed of a dense desmoplastic stroma, plays in tumor development, metastases and as a barrier to chemotherapy delivery has been elucidated over the years. More recently, a role for pancreatic cancer stem cells in resistance to chemotherapy and radiation therapy was discovered. In addition, a deeper understanding of the metabolic pathways responsible for adaptation of pancreatic cancer cells to hypoxic environments has significant implications for future therapeutic development.

While some of these discoveries have resulted in novel therapeutic targets and treatment strategies and others are currently being tested in preclinical trials, efficient and effective drug development to combat pancreatic ductal adenocarcinoma is a necessity for the future. The majority of clinical trials have been conducted in patients with advanced stage disease. In the future, it will be necessary to design clinical trials to enroll patients with earlier stages of pancreatic cancer in an attempt to cure their cancer before it can metastasize.

REFERENCES

- 1 **American Cancer Society.** Cancer Facts & Figures 2013. Atlanta: American Cancer Society, 2013: 25-32
- 2 **Kalager M,** Zelen M, Langmark F, Adami HO. Effect of screening mammography on breast-cancer mortality in Norway. *N Engl J Med* 2010; **363**: 1203-1210 [PMID: 20860502 DOI: 10.1056/NEJMoa1000727]
- 3 **DeSantis C,** Ma J, Bryan L, Jemal A. Breast cancer statistics, 2013. *CA Cancer J Clin* 2013; **64**: 52-62 [PMID: 24114568 DOI: 10.3322/caac.21203]
- 4 **Jemal A,** Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]
- 5 **Center MM,** Jemal A, Smith RA, Ward E. Worldwide variations in colorectal cancer. *CA Cancer J Clin* 2009; **59**: 366-378 [PMID: 19897840 DOI: 10.3322/caac.20038]
- 6 **Sener SF,** Fremgen A, Menck HR, Winchester DP. Pancreatic cancer: a report of treatment and survival trends for 100,313 patients diagnosed from 1985-1995, using the National Cancer Database. *J Am Coll Surg* 1999; **189**: 1-7 [PMID: 10401733 DOI: 10.1016/S1072-7515(99)00075-7]
- 7 **Simard EP,** Ward EM, Siegel R, Jemal A. Cancers with increasing incidence trends in the United States: 1999 through 2008. *CA Cancer J Clin* 2012; Epub ahead of print [PMID: 22281605 DOI: 10.3322/caac.20141]
- 8 **Siegel R,** Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012; **62**: 10-29 [PMID: 22237781 DOI: 10.3322/caac.20138]
- 9 **Petersen GM,** de Andrade M, Goggins M, Hruban RH, Bondy M, Korczak JF, Gallinger S, Lynch HT, Syngal S, Rabe KG, Seminara D, Klein AP. Pancreatic cancer genetic epidemiology consortium. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 704-710 [PMID: 16614112 DOI: 10.1158/1055-9965.EPI-05-0734]
- 10 **Blackford A,** Parmigiani G, Kensler TW, Wolfgang C, Jones

- S, Zhang X, Parsons DW, Lin JC, Leary RJ, Eshleman JR, Goggins M, Jaffee EM, Iacobuzio-Donahue CA, Maitra A, Klein A, Cameron JL, Olin K, Schulick R, Winter J, Vogelstein B, Velculescu VE, Kinzler KW, Hruban RH. Genetic mutations associated with cigarette smoking in pancreatic cancer. *Cancer Res* 2009; **69**: 3681-3688 [PMID: 19351817 DOI: 10.1158/0008-5472.CAN-09-0015]
- 11 **Shi C**, Hruban RH, Klein AP. Familial pancreatic cancer. *Arch Pathol Lab Med* 2009; **133**: 365-374 [PMID: 19260742]
 - 12 **Brune KA**, Lau B, Palmisano E, Canto M, Goggins MG, Hruban RH, Klein AP. Importance of age of onset in pancreatic cancer kindreds. *J Natl Cancer Inst* 2010; **102**: 119-126 [PMID: 20068195 DOI: 10.1093/jnci/djp466]
 - 13 **Genkinger JM**, Spiegelman D, Anderson KE, Bergkvist L, Bernstein L, van den Brandt PA, English DR, Freudenheim JL, Fuchs CS, Giles GG, Giovannucci E, Hankinson SE, Horn-Ross PL, Leitzmann M, Männistö S, Marshall JR, McCullough ML, Miller AB, Reding DJ, Robien K, Rohan TE, Schatzkin A, Stevens VL, Stolzenberg-Solomon RZ, Verhage BA, Wolk A, Ziegler RG, Smith-Warner SA. Alcohol intake and pancreatic cancer risk: a pooled analysis of fourteen cohort studies. *Cancer Epidemiol Biomarkers Prev* 2009; **18**: 765-776 [PMID: 19258474 DOI: 10.1158/1055-9965.EPI-08-0880]
 - 14 **Zhang J**, Dhakal IB, Gross MD, Lang NP, Kadlubar FF, Har-nack LJ, Anderson KE. Physical activity, diet, and pancreatic cancer: a population-based, case-control study in Minnesota. *Nutr Cancer* 2009; **61**: 457-465 [PMID: 19838917 DOI: 10.1080/01635580902718941]
 - 15 **Philip B**, Roland CL, Daniluk J, Liu Y, Chatterjee D, Gomez SB, Ji B, Huang H, Wang H, Fleming JB, Logsdon CD, Cruz-Monserrate Z. A high-fat diet activates oncogenic Kras and COX2 to induce development of pancreatic ductal adenocarcinoma in mice. *Gastroenterology* 2013; **145**: 1449-1458 [PMID: 23958541 DOI: 10.1053/j.gastro.2013.08.018]
 - 16 **Amaral AF**, Porta M, Silverman DT, Milne RL, Kogevinas M, Rothman N, Cantor KP, Jackson BP, Pumarega JA, López T, Carrato A, Guarner L, Real FX, Malats N. Pancreatic cancer risk and levels of trace elements. *Gut* 2012; **61**: 1583-1588 [PMID: 22184070 DOI: 10.1136/gutjnl-2011-301086]
 - 17 **Stathis A**, Moore MJ. Advanced pancreatic carcinoma: current treatment and future challenges. *Nat Rev Clin Oncol* 2010; **7**: 163-172 [PMID: 20101258 DOI: 10.1038/nrclinonc.2009.236]
 - 18 **Sheridan MB**, Ward J, Guthrie JA, Spencer JA, Craven CM, Wilson D, Guillou PJ, Robinson PJ. Dynamic contrast-enhanced MR imaging and dual-phase helical CT in the preoperative assessment of suspected pancreatic cancer: a comparative study with receiver operating characteristic analysis. *AJR Am J Roentgenol* 1999; **173**: 583-590 [PMID: 10470884 DOI: 10.2214/ajr.173.3.10470884]
 - 19 **Horton KM**, Fishman EK. Adenocarcinoma of the pancreas: CT imaging. *Radiol Clin North Am* 2002; **40**: 1263-1272 [PMID: 12479710 DOI: 10.1016/S0033-8389(02)00041-6]
 - 20 **Faria SC**, Tamm EP, Loyer EM, Szklaruk J, Choi H, Charnsangavej C. Diagnosis and staging of pancreatic tumors. *Semin Roentgenol* 2004; **39**: 397-411 [PMID: 15372753 DOI: 10.1016/j.ro.2004.06.012]
 - 21 **House MG**, Yeo CJ, Cameron JL, Campbell KA, Schulick RD, Leach SD, Hruban RH, Horton KM, Fishman EK, Lillemoe KD. Predicting resectability of peripapillary cancer with three-dimensional computed tomography. *J Gastrointest Surg* 2004; **8**: 280-288 [PMID: 15019924 DOI: 10.1016/j.gassur.2003.12.011]
 - 22 **Vachiranubhap B**, Kim YH, Balci NC, Semelka RC. Magnetic resonance imaging of adenocarcinoma of the pancreas. *Top Magn Reson Imaging* 2009; **20**: 3-9 [PMID: 19687720 DOI: 10.1097/RMR.0b013e3181b48392]
 - 23 **Tellez-Avila FI**, Chavez-Tapia NC, López-Arce G, Franco-Guzmán AM, Sosa-Lozano LA, Alfaro-Lara R, Chan-Núñez C, Giovannini M, Elizondo-Rivera J, Ramírez-Luna MA. Vascular invasion in pancreatic cancer: predictive values for endoscopic ultrasound and computed tomography imaging. *Pancreas* 2012; **41**: 636-638 [PMID: 22460727 DOI: 10.1097/MPA.0b013e31823e3632]
 - 24 **Sperti C**, Pasquali C, Bissoli S, Chierichetti F, Liessi G, Pedrazzoli S. Tumor relapse after pancreatic cancer resection is detected earlier by 18-FDG PET than by CT. *J Gastrointest Surg* 2010; **14**: 131-140 [PMID: 19777315 DOI: 10.1007/s11605-009-1010-8]
 - 25 **Warshaw AL**, Tepper JE, Shipley WU. Laparoscopy in the staging and planning of therapy for pancreatic cancer. *Am J Surg* 1986; **151**: 76-80 [PMID: 2936262 DOI: 10.1016/0002-9610(86)90015-2]
 - 26 **Bilimoria KY**, Bentrem DJ, Ko CY, Ritchey J, Stewart AK, Winchester DP, Talamonti MS. Validation of the 6th edition AJCC Pancreatic Cancer Staging System: report from the National Cancer Database. *Cancer* 2007; **110**: 738-744 [PMID: 17580363]
 - 27 **Bakkevold KE**, Arnesjø B, Kambestad B. Carcinoma of the pancreas and papilla of Vater--assessment of resectability and factors influencing resectability in stage I carcinomas. A prospective multicentre trial in 472 patients. *Eur J Surg Oncol* 1992; **18**: 494-507 [PMID: 1426302]
 - 28 **Porta M**, Fabregat X, Malats N, Guarner L, Carrato A, de Miguel A, Ruiz L, Jariod M, Costafreda S, Coll S, Alguacil J, Corominas JM, Solà R, Salas A, Real FX. Exocrine pancreatic cancer: symptoms at presentation and their relation to tumour site and stage. *Clin Transl Oncol* 2005; **7**: 189-197 [PMID: 15960930 DOI: 10.1007/BF02712816]
 - 29 **Chari ST**, Leibson CL, Rabe KG, Ransom J, de Andrade M, Petersen GM. Probability of pancreatic cancer following diabetes: a population-based study. *Gastroenterology* 2005; **129**: 504-511 [PMID: 16083707 DOI: 10.1016/j.gastro.2005.05.007]
 - 30 **Khorana AA**, Fine RL. Pancreatic cancer and thromboembolic disease. *Lancet Oncol* 2004; **5**: 655-663 [PMID: 15522652 DOI: 10.1016/S1470-2045(04)01606-7]
 - 31 **Pausch T**, Hartwig W, Hinz U, Swolana T, Bundy BD, Hackert T, Grenacher L, Büchler MW, Werner J. Cachexia but not obesity worsens the postoperative outcome after pancreatoduodenectomy in pancreatic cancer. *Surgery* 2012; **152**: S81-S88 [PMID: 22770957 DOI: 10.1016/j.surg.2012.05.028]
 - 32 **Langer P**, Kann PH, Fendrich V, Habbe N, Schneider M, Sina M, Slater EP, Heverhagen JT, Gress TM, Rothmund M, Bartsch DK. Five years of prospective screening of high-risk individuals from families with familial pancreatic cancer. *Gut* 2009; **58**: 1410-1418 [PMID: 19470496 DOI: 10.1136/gut.2008.171611]
 - 33 **Verna EC**, Hwang C, Stevens PD, Rotterdam H, Stavropoulos SN, Sy CD, Prince MA, Chung WK, Fine RL, Chabot JA, Frucht H. Pancreatic cancer screening in a prospective cohort of high-risk patients: a comprehensive strategy of imaging and genetics. *Clin Cancer Res* 2010; **16**: 5028-5037 [PMID: 20876795 DOI: 10.1158/1078-0432.CCR-09-3209]
 - 34 **Canto MI**, Hruban RH, Fishman EK, Kamel IR, Schulick R, Zhang Z, Topazian M, Takahashi N, Fletcher J, Petersen G, Klein AP, Axilbund J, Griffin C, Syngal S, Saltzman JR, Morteale KJ, Lee J, Tamm E, Vikram R, Bhosale P, Margolis D, Farrell J, Goggins M. Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. *Gastroenterology* 2012; **142**: 796-804; quiz e14-5 [PMID: 22245846]
 - 35 **Erkan M**, Hausmann S, Michalski CW, Fingerle AA, Dobritz M, Kleeff J, Friess H. The role of stroma in pancreatic cancer: diagnostic and therapeutic implications. *Nat Rev Gastroenterol Hepatol* 2012; **9**: 454-467 [PMID: 22710569 DOI: 10.1038/nrgastro.2012.115]
 - 36 **Goggins M**. Molecular markers of early pancreatic cancer. *J Clin Oncol* 2005; **23**: 4524-4531 [PMID: 16002843 DOI: 10.1200/JCO.2005.19.711]
 - 37 **Steinberg W**. The clinical utility of the CA 19-9 tumor-asso-

- ciated antigen. *Am J Gastroenterol* 1990; **85**: 350-355 [PMID: 2183589]
- 38 **Ballehaninna UK**, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence based appraisal. *J Gastrointest Oncol* 2012; **3**: 105-119 [PMID: 22811878 DOI: 10.3978/j.ssn.2078-6891.2011.021]
- 39 **Frebourg T**, Bercoff E, Manchon N, Senant J, Basuyau JP, Breton P, Janvresse A, Brunelle P, Bourreille J. The evaluation of CA 19-9 antigen level in the early detection of pancreatic cancer. A prospective study of 866 patients. *Cancer* 1988; **62**: 2287-2290 [PMID: 3179943]
- 40 **Nakai Y**, Isayama H, Sasaki T, Takahara N, Hamada T, Uchino R, Mizuno S, Miyabayashi K, Yamamoto K, Mohri D, Kogure H, Yamamoto N, Hirano K, Ijichi H, Tateishi K, Tada M, Koike K. A retrospective analysis of early CA19-9 change in salvage chemotherapy for refractory pancreatic cancer. *Cancer Chemother Pharmacol* 2013; **72**: 1291-1297 [PMID: 24121456 DOI: 10.1007/s00280-013-2313-8]
- 41 **Hidalgo M**. Pancreatic cancer. *N Engl J Med* 2010; **362**: 1605-1617 [PMID: 20427809 DOI: 10.1056/NEJMra0901557]
- 42 **Edge SB**, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010; **17**: 1471-1474 [PMID: 20180029]
- 43 **Chang KJ**, Nguyen P, Erickson RA, Durbin TE, Katz KD. The clinical utility of endoscopic ultrasound-guided fine-needle aspiration in the diagnosis and staging of pancreatic carcinoma. *Gastrointest Endosc* 1997; **45**: 387-393 [PMID: 9165320 DOI: 10.1016/S0016-5107(97)70149-4]
- 44 **Gress F**, Gottlieb K, Sherman S, Lehman G. Endoscopic ultrasonography-guided fine-needle aspiration biopsy of suspected pancreatic cancer. *Ann Intern Med* 2001; **134**: 459-464 [PMID: 11255521 DOI: 10.7326/0003-4819-134-6-200103200-0010]
- 45 **Perkins GL**, Slater ED, Sanders GK, Prichard JG. Serum tumor markers. *Am Fam Physician* 2003; **68**: 1075-1082 [PMID: 14524394]
- 46 **Goonetilleke KS**, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. *Eur J Surg Oncol* 2007; **33**: 266-270 [PMID: 17097848 DOI: 10.1016/j.ejso.2006.10.004]
- 47 **Tsutsumi K**, Kawamoto H, Hirao K, Sakakihara I, Yamamoto N, Noma Y, Fujii M, Kato H, Ogawa T, Ishida E, Kuwaki K, Nouse K, Okada H, Yamamoto K. Monitoring of CA19-9 and SPan-1 can facilitate the earlier confirmation of progressing pancreatic cancer during chemotherapy. *Pancreatology* 2012; **12**: 409-416 [PMID: 23127528 DOI: 10.1016/j.pan.2012.07.009]
- 48 **Chung MH**, Gupta RK, Bilchik AJ, Ye W, Yee R, Morton DL. Preoperative serum TA90-IC as an adjunct to serum CA 19-9 in the diagnosis of pancreatic malignancy: a pilot study. *Curr Surg* 2002; **59**: 194-198 [PMID: 16093131 DOI: 10.1016/S0149-7944(01)00594-3]
- 49 **Ishii H**, Okada S, Sato T, Wakasugi H, Saisho H, Furuse J, Ishikawa O, Matsuno S, Yokoyama S. CA 19-9 in evaluating the response to chemotherapy in advanced pancreatic cancer. *Hepatogastroenterology* 1997; **44**: 279-283 [PMID: 9058159]
- 50 **Wong D**, Ko AH, Hwang J, Venook AP, Bergsland EK, Tempero MA. Serum CA19-9 decline compared to radiographic response as a surrogate for clinical outcomes in patients with metastatic pancreatic cancer receiving chemotherapy. *Pancreas* 2008; **37**: 269-274 [PMID: 18815548 DOI: 10.1097/MPA.0b013e31816d8185]
- 51 **Montgomery RC**, Hoffman JP, Riley LB, Rogatko A, Ridge JA, Eisenberg BL. Prediction of recurrence and survival by post-resection CA 19-9 values in patients with adenocarcinoma of the pancreas. *Ann Surg Oncol* 1997; **4**: 551-556 [PMID: 9367020 DOI: 10.1007/BF02305535]
- 52 **Halm U**, Schumann T, Schiefke I, Witzigmann H, Mössner J, Keim V. Decrease of CA 19-9 during chemotherapy with gemcitabine predicts survival time in patients with advanced pancreatic cancer. *Br J Cancer* 2000; **82**: 1013-1016 [PMID: 10737382]
- 53 **Berger AC**, Garcia M, Hoffman JP, Regine WF, Abrams RA, Safran H, Konski A, Benson AB, MacDonald J, Willett CG. Postresection CA 19-9 predicts overall survival in patients with pancreatic cancer treated with adjuvant chemotherapy: a prospective validation by RTOG 9704. *J Clin Oncol* 2008; **26**: 5918-5922 [PMID: 19029412 DOI: 10.1200/JCO.2008.18.6288]
- 54 **Almoguera C**, Shibata D, Forrester K, Martin J, Arnheim N, Perucho M. Most human carcinomas of the exocrine pancreas contain mutant c-K-ras genes. *Cell* 1988; **53**: 549-554 [PMID: 2453289 DOI: 10.1016/0092-8674(88)90571-5]
- 55 **Vogelstein B**, Kinzler KW. Cancer genes and the pathways they control. *Nat Med* 2004; **10**: 789-799 [PMID: 15286780 DOI: 10.1038/nm1087]
- 56 **Hruban RH**, Maitra A, Goggins M. Update on pancreatic intraepithelial neoplasia. *Int J Clin Exp Pathol* 2008; **1**: 306-316 [PMID: 18787611]
- 57 **Pellegata NS**, Sessa F, Renault B, Bonato M, Leone BE, Solcia E, Ranzani GN. K-ras and p53 gene mutations in pancreatic cancer: ductal and nonductal tumors progress through different genetic lesions. *Cancer Res* 1994; **54**: 1556-1560 [PMID: 8137263]
- 58 **Hezel AF**, Kimmelman AC, Stanger BZ, Bardeesy N, Depinho RA. Genetics and biology of pancreatic ductal adenocarcinoma. *Genes Dev* 2006; **20**: 1218-1249 [PMID: 16702400 DOI: 10.1101/gad.1415606]
- 59 **Maitra A**, Hruban RH. Pancreatic cancer. *Annu Rev Pathol* 2008; **3**: 157-188 [PMID: 18039136 DOI: 10.1146/annurev.pathmechdis.3.121806.154305]
- 60 **Bardeesy N**, Cheng KH, Berger JH, Chu GC, Pahler J, Olson P, Hezel AF, Horner J, Lauwers GY, Hanahan D, DePinho RA. Smad4 is dispensable for normal pancreas development yet critical in progression and tumor biology of pancreas cancer. *Genes Dev* 2006; **20**: 3130-3146 [PMID: 17114584 DOI: 10.1101/gad.1478706]
- 61 **Takaori K**, Hruban RH, Maitra A, Tanigawa N. Pancreatic intraepithelial neoplasia. *Pancreas* 2004; **28**: 257-262 [PMID: 15084967 DOI: 10.1097/00006676-200404000-00008]
- 62 **Gedde-Dahl T**, Eriksen JA, Thorsby E, Gaudernack G. T-cell responses against products of oncogenes: generation and characterization of human T-cell clones specific for p21 ras-derived synthetic peptides. *Hum Immunol* 1992; **33**: 266-274 [PMID: 1639630 DOI: 10.1016/0198-8859(92)90334-J]
- 63 **Fossum B**, Gedde-Dahl T, Hansen T, Eriksen JA, Thorsby E, Gaudernack G. Overlapping epitopes encompassing a point mutation (12 Gly--> Arg) in p21 ras can be recognized by HLA-DR, -DP and -DQ restricted T cells. *Eur J Immunol* 1993; **23**: 2687-2691 [PMID: 7691613 DOI: 10.1002/eji.1830231045]
- 64 **Gjertsen MK**, Bakka A, Breivik J, Saeterdal I, Solheim BG, Søreide O, Thorsby E, Gaudernack G. Vaccination with mutant ras peptides and induction of T-cell responsiveness in pancreatic carcinoma patients carrying the corresponding RAS mutation. *Lancet* 1995; **346**: 1399-1400 [PMID: 7475823 DOI: 10.1016/S0140-6736(95)92408-6]
- 65 **Abou-Alfa GK**, Chapman PB, Feilchenfeldt J, Brennan MF, Capanu M, Gansukh B, Jacobs G, Levin A, Neville D, Kelsen DP, O'Reilly EM. Targeting mutated K-ras in pancreatic adenocarcinoma using an adjuvant vaccine. *Am J Clin Oncol* 2011; **34**: 321-325 [PMID: 20686403 DOI: 10.1097/COC.0b013e3181e84b1f]
- 66 **Wedén S**, Klemp M, Gladhaug IP, Møller M, Eriksen JA, Gaudernack G, Buanes T. Long-term follow-up of patients with resected pancreatic cancer following vaccination against mutant K-ras. *Int J Cancer* 2011; **128**: 1120-1128 [PMID: 20473937 DOI: 10.1002/ijc.25449]
- 67 **Redston MS**, Caldas C, Seymour AB, Hruban RH, da Costa L, Yeo CJ, Kern SE. p53 mutations in pancreatic carcinoma

- and evidence of common involvement of homocopolymer tracts in DNA microdeletions. *Cancer Res* 1994; **54**: 3025-3033 [PMID: 8187092]
- 68 **Olive KP**, Tuveson DA, Ruhe ZC, Yin B, Willis NA, Bronson RT, Crowley D, Jacks T. Mutant p53 gain of function in two mouse models of Li-Fraumeni syndrome. *Cell* 2004; **119**: 847-860 [PMID: 15607980 DOI: 10.1016/j.cell.2004.11.004]
 - 69 **Morton JP**, Timpson P, Karim SA, Ridgway RA, Athineos D, Doyle B, Jamieson NB, Oien KA, Lowy AM, Brunton VG, Frame MC, Evans TR, Sansom OJ. Mutant p53 drives metastasis and overcomes growth arrest/senescence in pancreatic cancer. *Proc Natl Acad Sci USA* 2010; **107**: 246-251 [PMID: 20018721 DOI: 10.1073/pnas.0908428107]
 - 70 **Caldas C**, Hahn SA, da Costa LT, Redston MS, Schutte M, Seymour AB, Weinstein CL, Hruban RH, Yeo CJ, Kern SE. Frequent somatic mutations and homozygous deletions of the p16 (MTS1) gene in pancreatic adenocarcinoma. *Nat Genet* 1994; **8**: 27-32 [PMID: 7726912 DOI: 10.1038/ng0994-27]
 - 71 **Schutte M**, Hruban RH, Geradts J, Maynard R, Hilgers W, Rabindran SK, Moskaluk CA, Hahn SA, Schwarte-Waldhoff I, Schmiegel W, Baylin SB, Kern SE, Herman JG. Abrogation of the Rb/p16 tumor-suppressive pathway in virtually all pancreatic carcinomas. *Cancer Res* 1997; **57**: 3126-3130 [PMID: 9242437]
 - 72 **Hahn SA**, Hoque AT, Moskaluk CA, da Costa LT, Schutte M, Rozenblum E, Seymour AB, Weinstein CL, Yeo CJ, Hruban RH, Kern SE. Homozygous deletion map at 18q21.1 in pancreatic cancer. *Cancer Res* 1996; **56**: 490-494 [PMID: 8564959]
 - 73 **Yachida S**, White CM, Naito Y, Zhong Y, Brosnan JA, Macgregor-Das AM, Morgan RA, Saunders T, Laheru DA, Herman JM, Hruban RH, Klein AP, Jones S, Velculescu V, Wolfgang CL, Iacobuzio-Donahue CA. Clinical significance of the genetic landscape of pancreatic cancer and implications for identification of potential long-term survivors. *Clin Cancer Res* 2012; **18**: 6339-6347 [PMID: 22991414 DOI: 10.1158/1078-0432.CCR-12-1215]
 - 74 **Hansel DE**, Kern SE, Hruban RH. Molecular pathogenesis of pancreatic cancer. *Annu Rev Genomics Hum Genet* 2003; **4**: 237-256 [PMID: 14527303 DOI: 10.1146/annurev.genom.4.070802.110341]
 - 75 **Biankin AV**, Waddell N, Kassahn KS, Gingras MC, Muthuswamy LB, Johns AL, Miller DK, Wilson PJ, Patch AM, Wu J, Chang DK, Cowley MJ, Gardiner BB, Song S, Harliwong I, Idrisoglu S, Nourse C, Nourbakhsh E, Manning S, Wani S, Gongora M, Pajic M, Scarlett CJ, Gill AJ, Pinho AV, Rooman I, Anderson M, Holmes O, Leonard C, Taylor D, Wood S, Xu Q, Nones K, Fink JL, Christ A, Bruxner T, Cloonan N, Kolle G, Newell F, Pineles M, Mead RS, Humphris JL, Kaplan W, Jones MD, Colvin EK, Nagrial AM, Humphrey ES, Chou A, Chin VT, Chantrill LA, Mawson A, Samra JS, Kench JG, Lovell JA, Daly RJ, Merrett ND, Toon C, Epari K, Nguyen NQ, Barbour A, Zeps N, Kakkar N, Zhao F, Wu YQ, Wang M, Muzny DM, Fisher WE, Brunicardi FC, Hodges SE, Reid JG, Drummond J, Chang K, Han Y, Lewis LR, Dinh H, Buhay CJ, Beck T, Timms L, Sam M, Begley K, Brown A, Pai D, Panchal A, Buchner N, De Borja R, Denroche RE, Yung CK, Serra S, Onetto N, Mukhopadhyay D, Tsao MS, Shaw PA, Petersen GM, Gallinger S, Hruban RH, Maitra A, Iacobuzio-Donahue CA, Schlick RD, Wolfgang CL, Morgan RA, Lawlor RT, Capelli P, Corbo V, Scardoni M, Tortora G, Tempero MA, Mann KM, Jenkins NA, Perez-Mancera PA, Adams DJ, Largaespada DA, Wessels LF, Rust AG, Stein LD, Tuveson DA, Copeland NG, Musgrove EA, Scarpa A, Eshleman JR, Hudson TJ, Sutherland RL, Wheeler DA, Pearson JV, McPherson JD, Gibbs RA, Grimmond SM. Pancreatic cancer genomes reveal aberrations in axon guidance pathway genes. *Nature* 2012; **491**: 399-405 [PMID: 23103869 DOI: 10.1038/nature11547]
 - 76 **Pérez-Mancera PA**, Rust AG, van der Weyden L, Kristiansen G, Li A, Sarver AL, Silverstein KA, Grützmann R, Aust D, Rümmele P, Knösel T, Herd C, Stemple DL, Kettleborough R, Brosnan JA, Li A, Morgan R, Knight S, Yu J, Stegeman S, Collier LS, ten Hoeve JJ, de Ridder J, Klein AP, Goggins M, Hruban RH, Chang DK, Biankin AV, Grimmond SM, Wessels LF, Wood SA, Iacobuzio-Donahue CA, Pilarsky C, Largaespada DA, Adams DJ, Tuveson DA. The deubiquitinase USP9X suppresses pancreatic ductal adenocarcinoma. *Nature* 2012; **486**: 266-270 [PMID: 22699621]
 - 77 **Jones S**, Zhang X, Parsons DW, Lin JC, Leary RJ, Angenendt P, Mankoo P, Carter H, Kamiyama H, Jimeno A, Hong SM, Fu B, Lin MT, Calhoun ES, Kamiyama M, Walter K, Nikolskaya T, Nikolsky Y, Hartigan J, Smith DR, Hidalgo M, Leach SD, Klein AP, Jaffee EM, Goggins M, Maitra A, Iacobuzio-Donahue C, Eshleman JR, Kern SE, Hruban RH, Karchin R, Papadopoulos N, Parmigiani G, Vogelstein B, Velculescu VE, Kinzler KW. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. *Science* 2008; **321**: 1801-1806 [PMID: 18772397 DOI: 10.1126/science.1164368]
 - 78 **Chu GC**, Kimmelman AC, Hezel AF, DePinho RA. Stromal biology of pancreatic cancer. *J Cell Biochem* 2007; **101**: 887-907 [PMID: 17266048 DOI: 10.1002/jcb.21209]
 - 79 **Neesse A**, Michl P, Frese KK, Feig C, Cook N, Jacobetz MA, Lolkema MP, Buchholz M, Olive KP, Gress TM, Tuveson DA. Stromal biology and therapy in pancreatic cancer. *Gut* 2011; **60**: 861-868 [PMID: 20966025 DOI: 10.1136/gut.2010.226092]
 - 80 **Collins MA**, Bednar F, Zhang Y, Brisset JC, Galbán S, Galbán CJ, Rakshit S, Flannagan KS, Adsay NV, Pasca di Magliano M. Oncogenic Kras is required for both the initiation and maintenance of pancreatic cancer in mice. *J Clin Invest* 2012; **122**: 639-653 [PMID: 2232209 DOI: 10.1172/JCI59227]
 - 81 **Ying H**, Kimmelman AC, Lyssiotis CA, Hua S, Chu GC, Fletcher-Sananikone E, Locasale JW, Son J, Zhang H, Colloff JL, Yan H, Wang W, Chen S, Viale A, Zheng H, Paik JH, Lim C, Guimaraes AR, Martin ES, Chang J, Hezel AF, Perry SR, Hu J, Gan B, Xiao Y, Asara JM, Weissleder R, Wang YA, Chin L, Cantley LC, DePinho RA. Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism. *Cell* 2012; **149**: 656-670 [PMID: 22541435 DOI: 10.1016/j.cell.2012.01.058]
 - 82 **Nolan-Stevaux O**, Lau J, Truitt ML, Chu GC, Hebrok M, Fernández-Zapico ME, Hanahan D. GLI1 is regulated through Smoothed-independant mechanisms in neoplastic pancreatic ducts and mediates PDAC cell survival and transformation. *Genes Dev* 2009; **23**: 24-36 [PMID: 19136624 DOI: 10.1101/gad.1753809]
 - 83 **Bailey JM**, Swanson BJ, Hamada T, Eggers JP, Singh PK, Caffery T, Ouellette MM, Hollingsworth MA. Sonic hedgehog promotes desmoplasia in pancreatic cancer. *Clin Cancer Res* 2008; **14**: 5995-6004 [PMID: 18829478 DOI: 10.1158/1078-0432.CCR-08-0291]
 - 84 **Tian H**, Callahan CA, DuPree KJ, Darbonne WC, Ahn CP, Scales SJ, de Sauvage FJ. Hedgehog signaling is restricted to the stromal compartment during pancreatic carcinogenesis. *Proc Natl Acad Sci USA* 2009; **106**: 4254-4259 [PMID: 19246386 DOI: 10.1073/pnas.0813203106]
 - 85 **Olive KP**, Jacobetz MA, Davidson CJ, Gopinathan A, McIntyre D, Honess D, Madhu B, Goldgraben MA, Caldwell ME, Allard D, Frese KK, Denicola G, Feig C, Combs C, Winter SP, Ireland-Zecchini H, Reichelt S, Howat WJ, Chang A, Dhara M, Wang L, Rückert F, Grützmann R, Pilarsky C, Izradjene K, Hingorani SR, Huang P, Davies SE, Plunkett W, Egorin M, Hruban RH, Whitebread N, McGovern K, Adams J, Iacobuzio-Donahue C, Griffiths J, Tuveson DA. Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. *Science* 2009; **324**: 1457-1461 [PMID: 19460966 DOI: 10.1126/science.1171362]
 - 86 **Komar G**, Kauhanen S, Liukko K, Seppänen M, Kajander S, Ovaska J, Nuutila P, Minn H. Decreased blood flow with increased metabolic activity: a novel sign of pancreatic tumor

- aggressiveness. *Clin Cancer Res* 2009; **15**: 5511-5517 [PMID: 19706808 DOI: 10.1158/1078-0432.CCR-09-0414]
- 87 **Bayne LJ**, Beatty GL, Jhala N, Clark CE, Rhim AD, Stanger BZ, Vonderheide RH. Tumor-derived granulocyte-macrophage colony-stimulating factor regulates myeloid inflammation and T cell immunity in pancreatic cancer. *Cancer Cell* 2012; **21**: 822-835 [PMID: 22698406 DOI: 10.1016/j.ccr.2012.04.025]
- 88 **Pylayeva-Gupta Y**, Lee KE, Hajdu CH, Miller G, Bar-Sagi D. Oncogenic Kras-induced GM-CSF production promotes the development of pancreatic neoplasia. *Cancer Cell* 2012; **21**: 836-847 [PMID: 22698407 DOI: 10.1016/j.ccr.2012.04.024]
- 89 **Li D**, Xie K, Wolff R, Abbruzzese JL. Pancreatic cancer. *Lancet* 2004; **363**: 1049-1057 [PMID: 15051286 DOI: 10.1016/S0140-6736(04)15841-8]
- 90 **Wagner M**, Redaelli C, Lietz M, Seiler CA, Friess H, Büchler MW. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. *Br J Surg* 2004; **91**: 586-594 [PMID: 15122610 DOI: 10.1002/bjs.4484]
- 91 **Uchida H**, Shibata K, Iwaki K, Kai S, Ohta M, Kitano S. Ampullary cancer and preoperative jaundice: possible indication of the minimal surgery. *Hepatogastroenterology* 2009; **56**: 1194-1198 [PMID: 19760968]
- 92 **van der Gaag NA**, Kloek JJ, de Castro SM, Busch OR, van Gulik TM, Gouma DJ. Preoperative biliary drainage in patients with obstructive jaundice: history and current status. *J Gastrointest Surg* 2009; **13**: 814-820 [PMID: 18726134 DOI: 10.1007/s11605-008-0618-4]
- 93 **Sewnath ME**, Karsten TM, Prins MH, Rauws EJ, Obertop H, Gouma DJ. A meta-analysis on the efficacy of preoperative biliary drainage for tumors causing obstructive jaundice. *Ann Surg* 2002; **236**: 17-27 [PMID: 12131081 DOI: 10.1097/0000658-200207000-00005]
- 94 **van der Gaag NA**, Rauws EA, van Eijck CH, Bruno MJ, van der Harst E, Kubben FJ, Gerritsen JJ, Greve JW, Gerhards MF, de Hingh IH, Klinkenbijl JH, Nio CY, de Castro SM, Busch OR, van Gulik TM, Bossuyt PM, Gouma DJ. Preoperative biliary drainage for cancer of the head of the pancreas. *N Engl J Med* 2010; **362**: 129-137 [PMID: 20071702 DOI: 10.1056/NEJMoa0903230]
- 95 **Jenkins LJ**, Parmar AD, Han Y, Duncan CB, Sheffield KM, Brown KM, Riall TS. Current trends in preoperative biliary stenting in patients with pancreatic cancer. *Surgery* 2013; **154**: 179-189 [PMID: 23889947 DOI: 10.1016/j.surg.2013.03.016]
- 96 **Riediger H**, Keck T, Wellner U, zur Hausen A, Adam U, Hopt UT, Makowiec F. The lymph node ratio is the strongest prognostic factor after resection of pancreatic cancer. *J Gastrointest Surg* 2009; **13**: 1337-1344 [PMID: 19418101 DOI: 10.1007/s11605-009-0919-2]
- 97 **Wasif N**, Ko CY, Farrell J, Wainberg Z, Hines OJ, Reber H, Tomlinson JS. Impact of tumor grade on prognosis in pancreatic cancer: should we include grade in AJCC staging? *Ann Surg Oncol* 2010; **17**: 2312-2320 [PMID: 20422460 DOI: 10.1245/s10434-010-1071-7]
- 98 **Fortner JG**, Klimstra DS, Senie RT, Maclean BJ. Tumor size is the primary prognosticator for pancreatic cancer after regional pancreatectomy. *Ann Surg* 1996; **223**: 147-153 [PMID: 8597508 DOI: 10.1097/0000658-199602000-00006]
- 99 **Skipworth RJ**, Parks RW, Stephens NA, Graham C, Brewster DH, Garden OJ, Paterson-Brown S. The relationship between hospital volume and post-operative mortality rates for upper gastrointestinal cancer resections: Scotland 1982-2003. *Eur J Surg Oncol* 2010; **36**: 141-147 [PMID: 19879717 DOI: 10.1016/j.ejso.2009.10.004]
- 100 **Finks JF**, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. *N Engl J Med* 2011; **364**: 2128-2137 [PMID: 21631325 DOI: 10.1056/NEJMsa1010705]
- 101 **Lemmens VE**, Bosscha K, van der Schelling G, Brennk-meijer S, Coebergh JW, de Hingh IH. Improving outcome for patients with pancreatic cancer through centralization. *Br J Surg* 2011; **98**: 1455-1462 [PMID: 21717423 DOI: 10.1002/bjs.7581]
- 102 **Gillen S**, Schuster T, Meyer Zum Büschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med* 2010; **7**: e1000267 [PMID: 20422030 DOI: 10.1371/journal.pmed.1000267]
- 103 **McClaine RJ**, Lowy AM, Sussman JJ, Schmulowitz N, Grisell DL, Ahmad SA. Neoadjuvant therapy may lead to successful surgical resection and improved survival in patients with borderline resectable pancreatic cancer. *HPB (Oxford)* 2010; **12**: 73-79 [PMID: 20495649 DOI: 10.1111/j.1477-2574.2009.00136.x]
- 104 **Le Scodan R**, Mornex F, Partensky C, Mercier C, Valette PJ, Ychou M, Roy P, Scoazec JY. Histopathological response to preoperative chemoradiation for resectable pancreatic adenocarcinoma: the French Phase II FFCD 9704-SFRO Trial. *Am J Clin Oncol* 2008; **31**: 545-552 [PMID: 19060585 DOI: 10.1097/COC.0b013e318172d5c5]
- 105 **White RR**, Xie HB, Gottfried MR, Czito BG, Hurwitz HI, Morse MA, Blobe GC, Paulson EK, Baillie J, Branch MS, Jowell PS, Clary BM, Pappas TN, Tyler DS. Significance of histological response to preoperative chemoradiotherapy for pancreatic cancer. *Ann Surg Oncol* 2005; **12**: 214-221 [PMID: 15827813 DOI: 10.1245/ASO.2005.03.105]
- 106 **Kim HJ**, Czischke K, Brennan MF, Conlon KC. Does neoadjuvant chemoradiation downstage locally advanced pancreatic cancer? *J Gastrointest Surg* 2002; **6**: 763-769 [PMID: 12399067 DOI: 10.1016/S1091-255X(02)00017-3]
- 107 **Massucco P**, Capussotti L, Magnino A, Sperti E, Gatti M, Muratore A, Sgotto E, Gabriele P, Aglietta M. Pancreatic resections after chemoradiotherapy for locally advanced ductal adenocarcinoma: analysis of perioperative outcome and survival. *Ann Surg Oncol* 2006; **13**: 1201-1208 [PMID: 16955382 DOI: 10.1245/s10434-006-9032-x]
- 108 **Neoptolemos JP**, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, Padbury R, Moore MJ, Gallinger S, Mariette C, Wente MN, Izbicki JR, Friess H, Lerch MM, Dervenis C, Oláh A, Butturini G, Doi R, Lind PA, Smith D, Valle JW, Palmer DH, Buckels JA, Thompson J, McKay CJ, Rawcliffe CL, Büchler MW. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA* 2010; **304**: 1073-1081 [PMID: 20823433 DOI: 10.1001/jama.2010.1275]
- 109 **Dineen SP**, Roland CL, Greer R, Carbon JG, Toombs JE, Gupta P, Bardeesy N, Sun H, Williams N, Minna JD, Brekken RA. Smac mimetic increases chemotherapy response and improves survival in mice with pancreatic cancer. *Cancer Res* 2010; **70**: 2852-2861 [PMID: 20332237 DOI: 10.1158/0008-5472.CAN-09-3892]
- 110 **Hwang JH**, Voortman J, Giovannetti E, Steinberg SM, Leon LG, Kim YT, Funel N, Park JK, Kim MA, Kang GH, Kim SW, Del Chiaro M, Peters GJ, Giaccone G. Identification of microRNA-21 as a biomarker for chemoresistance and clinical outcome following adjuvant therapy in resectable pancreatic cancer. *PLoS One* 2010; **5**: e10630 [PMID: 20498843 DOI: 10.1371/journal.pone.0010630]
- 111 **Harikumar KB**, Kunnumakkara AB, Sethi G, Diagaradjane P, Anand P, Pandey MK, Gelovani J, Krishnan S, Guha S, Aggarwal BB. Resveratrol, a multitargeted agent, can enhance antitumor activity of gemcitabine in vitro and in orthotopic mouse model of human pancreatic cancer. *Int J Cancer* 2010; **127**: 257-268 [PMID: 19908231]
- 112 **Cunningham D**, Chau I, Stocken DD, Valle JW, Smith D, Steward W, Harper PG, Dunn J, Tudur-Smith C, West J, Falk S, Crellin A, Adab F, Thompson J, Leonard P, Ostrowski J, Eatock M, Scheithauer W, Herrmann R, Neoptolemos JP.

- Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol* 2009; **27**: 5513-5518 [PMID: 19858379 DOI: 10.1200/JCO.2009.24.2446]
- 113 **Banerjee S**, Kaseb AO, Wang Z, Kong D, Mohammad M, Padhye S, Sarkar FH, Mohammad RM. Antitumor activity of gemcitabine and oxaliplatin is augmented by thymoquinone in pancreatic cancer. *Cancer Res* 2009; **69**: 5575-5583 [PMID: 19549912 DOI: 10.1158/0008-5472.CAN-08-4235]
 - 114 **Baylot V**, Andrieu C, Katsogiannou M, Taieb D, Garcia S, Giusiano S, Acunzo J, Iovanna J, Gleave M, Garrido C, Rocchi P. OGX-427 inhibits tumor progression and enhances gemcitabine chemotherapy in pancreatic cancer. *Cell Death Dis* 2011; **2**: e221 [PMID: 22012255 DOI: 10.1038/cddis.2011.104]
 - 115 **Kanai M**, Yoshimura K, Asada M, Imaizumi A, Suzuki C, Matsumoto S, Nishimura T, Mori Y, Masui T, Kawaguchi Y, Yanagihara K, Yazumi S, Chiba T, Guha S, Aggarwal BB. A phase I/II study of gemcitabine-based chemotherapy plus curcumin for patients with gemcitabine-resistant pancreatic cancer. *Cancer Chemother Pharmacol* 2011; **68**: 157-164 [PMID: 20859741 DOI: 10.1007/s00280-010-1470-2]
 - 116 **Farrell JJ**, Elsaleh H, Garcia M, Lai R, Ammar A, Regine WF, Abrams R, Benson AB, Macdonald J, Cass CE, Dicker AP, Mackey JR. Human equilibrative nucleoside transporter 1 levels predict response to gemcitabine in patients with pancreatic cancer. *Gastroenterology* 2009; **136**: 187-195 [PMID: 18992248 DOI: 10.1053/j.gastro.2008.09.067]
 - 117 **Fujita H**, Ohuchida K, Mizumoto K, Itaba S, Ito T, Nakata K, Yu J, Kayashima T, Souzaki R, Tajiri T, Manabe T, Ohtsuka T, Tanaka M. Gene expression levels as predictive markers of outcome in pancreatic cancer after gemcitabine-based adjuvant chemotherapy. *Neoplasia* 2010; **12**: 807-817 [PMID: 20927319]
 - 118 **Burris HA**, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997; **15**: 2403-2413 [PMID: 9196156]
 - 119 **Heinemann V**, Boeck S, Hinke A, Labianca R, Louvet C. Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. *BMC Cancer* 2008; **8**: 82 [PMID: 18373843 DOI: 10.1186/11471-2407-8-82]
 - 120 **Ren M**, Cordio S, Milandri C, Passoni P, Bonetto E, Oliani C, Luppi G, Nicoletti R, Galli L, Bordonaro R, Passardi A, Zerbi A, Balzano G, Aldrighetti L, Staudacher C, Villa E, Di Carlo V. Gemcitabine versus cisplatin, epirubicin, fluorouracil, and gemcitabine in advanced pancreatic cancer: a randomised controlled multicentre phase III trial. *Lancet Oncol* 2005; **6**: 369-376 [PMID: 15925814 DOI: 10.1016/S1470-2045(05)70175-3]
 - 121 **Conroy T**, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; **364**: 1817-1825 [PMID: 21561347 DOI: 10.1056/NEJMoa1011923]
 - 122 **Moore MJ**, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, Campos D, Lim R, Ding K, Clark G, Voskoglou-Nomikos T, Ptasynski M, Parulekar W. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007; **25**: 1960-1966 [PMID: 17452677 DOI: 10.1200/JCO.2006.07.9525]
 - 123 **Edmonds C**, Cengel KA. Tumor-Stroma interactions in pancreatic cancer: Will this SPARC prove a raging fire? *Cancer Biol Ther* 2008; **7**: 1816-1817 [PMID: 19029794 DOI: 10.4161/cbt.7.11.7285]
 - 124 **Infante JR**, Matsubayashi H, Sato N, Tonascia J, Klein AP, Riall TA, Yeo C, Iacobuzio-Donahue C, Goggins M. Peritumoral fibroblast SPARC expression and patient outcome with resectable pancreatic adenocarcinoma. *J Clin Oncol* 2007; **25**: 319-325 [PMID: 17235047 DOI: 10.1200/JCO.2006.07.8824]
 - 125 **Von Hoff DD**, Ramanathan RK, Borad MJ, Laheru DA, Smith LS, Wood TE, Korn RL, Desai N, Trieu V, Iglesias JL, Zhang H, Soon-Shiong P, Shi T, Rajeshkumar NV, Maitra A, Hidalgo M. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. *J Clin Oncol* 2011; **29**: 4548-4554 [PMID: 21969517 DOI: 10.1200/JCO.2011.36.5742]
 - 126 **Caridi G**, Gigante M, Ravani P, Trivelli A, Barbano G, Scolari F, Dagnino M, Murer L, Murtas C, Edefonti A, Allegri L, Amore A, Coppo R, Emma F, De Palo T, Penza R, Gesualdo L, Ghiggeri GM. Clinical features and long-term outcome of nephrotic syndrome associated with heterozygous NPHS1 and NPHS2 mutations. *Clin J Am Soc Nephrol* 2009; **4**: 1065-1072 [PMID: 19406966 DOI: 10.2215/CJN.03910808]
 - 127 **Custodio A**, Puente J, Sastre J, Díaz-Rubio E. Second-line therapy for advanced pancreatic cancer: a review of the literature and future directions. *Cancer Treat Rev* 2009; **35**: 676-684 [PMID: 19758760 DOI: 10.1016/j.ctrv.2009.08.012]
 - 128 **Boeck S**, Ankerst DP, Heinemann V. The role of adjuvant chemotherapy for patients with resected pancreatic cancer: systematic review of randomized controlled trials and meta-analysis. *Oncology* 2007; **72**: 314-321 [PMID: 18187951 DOI: 10.1159/000113054]
 - 129 **Lim KH**, Chung E, Khan A, Cao D, Linehan D, Ben-Josef E, Wang-Gillam A. Neoadjuvant therapy of pancreatic cancer: the emerging paradigm? *Oncologist* 2012; **17**: 192-200 [PMID: 22250057 DOI: 10.1634/theoncologist.2011-0268]
 - 130 **Evans DB**, Rich TA, Byrd DR, Cleary KR, Connelly JH, Levin B, Charnsangavej C, Fenoglio CJ, Ames FC. Preoperative chemoradiation and pancreaticoduodenectomy for adenocarcinoma of the pancreas. *Arch Surg* 1992; **127**: 1335-1339 [PMID: 1359851 DOI: 10.1001/archsurg.1992.01420110083017]
 - 131 **Pisters PW**, Abbruzzese JL, Janjan NA, Cleary KR, Charnsangavej C, Goswitz MS, Rich TA, Raijman I, Wolff RA, Lenzi R, Lee JE, Evans DB. Rapid-fractionation preoperative chemoradiation, pancreaticoduodenectomy, and intraoperative radiation therapy for resectable pancreatic adenocarcinoma. *J Clin Oncol* 1998; **16**: 3843-3850 [PMID: 9850029]
 - 132 **Krishnan S**, Rana V, Evans DB, Varadhachary G, Das P, Bhatia S, Delclos ME, Janjan NA, Wolff RA, Crane CH, Pisters PW. Role of adjuvant chemoradiation therapy in adenocarcinomas of the ampulla of Vater. *Int J Radiat Oncol Biol Phys* 2008; **70**: 735-743 [PMID: 17980502 DOI: 10.1016/j.ijrobp.2007.07.2327]
 - 133 **Hong TS**, Ryan DP, Blaszkowsky LS, Mamon HJ, Kwak EL, Mino-Kenudson M, Adams J, Yeap B, Winrich B, DeLaney TF, Fernandez-Del Castillo C. Phase I study of preoperative short-course chemoradiation with proton beam therapy and capecitabine for resectable pancreatic ductal adenocarcinoma of the head. *Int J Radiat Oncol Biol Phys* 2011; **79**: 151-157 [PMID: 20421151 DOI: 10.1016/j.ijrobp.2009.10.061]
 - 134 **Hadley DW**, Jenkins JF, Steinberg S, Liewehr D, Moller S, Martin JC, Calzone KA, Soballe PW, Kirsch IR. Perceptions of cancer risks and predictors of colon and endometrial cancer screening in women undergoing genetic testing for Lynch syndrome. *J Clin Oncol* 2008; **26**: 948-954 [PMID: 18281669 DOI: 10.1200/JCO.2007.13.9014]
 - 135 **Patel M**, Hoffe S, Malafa M, Hodul P, Klapman J, Centeno B, Kim J, Helm J, Valone T, Springett G. Neoadjuvant GTX chemotherapy and IMRT-based chemoradiation for borderline resectable pancreatic cancer. *J Surg Oncol* 2011; **104**: 155-161

- [PMID: 21520097 DOI: 10.1002/jso.21954]
- 136 **Yeo CJ**, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA, Hruban RH, Ord SE, Sauter PK, Coleman J, Zahurak ML, Grochow LB, Abrams RA. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. *Ann Surg* 1997; **226**: 248-57; discussion 257-60 [PMID: 9339931 DOI: 10.1097/0000658-199709000-00004]
 - 137 **Neoptolemos JP**, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, Beger H, Fernandez-Cruz L, Dervenis C, Lacaine F, Falconi M, Pederzoli P, Pap A, Spooner D, Kerr DJ, Büchler MW. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med* 2004; **350**: 1200-1210 [PMID: 15028824 DOI: 10.1056/NEJMoa032295]
 - 138 **Regine WF**, Winter KA, Abrams R, Safran H, Hoffman JP, Konski A, Benson AB, Macdonald JS, Rich TA, Willett CG. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/ RTOG 9704 phase III trial. *Ann Surg Oncol* 2011; **18**: 1319-1326 [PMID: 21499862 DOI: 10.1245/s10434-011-1630-6]
 - 139 **Oettle H**, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, Schramm H, Fahlke J, Zuelke C, Burkart C, Gutberlet K, Kettner E, Schmalenberg H, Weigang-Koehler K, Bechstein WO, Niedergethmann M, Schmidt-Wolf I, Roll L, Doerken B, Riess H. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA* 2007; **297**: 267-277 [PMID: 17227978 DOI: 10.1001/jama.297.3.267]
 - 140 **Yeo CJ**, Abrams RA, Grochow LB, Sohn TA, Ord SE, Hruban RH, Zahurak ML, Dooley WC, Coleman J, Sauter PK, Pitt HA, Lillemoe KD, Cameron JL. Pancreaticoduodenectomy for pancreatic adenocarcinoma: postoperative adjuvant chemoradiation improves survival. A prospective, single-institution experience. *Ann Surg* 1997; **225**: 621-33; discussion 633-6 [PMID: 9193189 DOI: 10.1097/0000658-199705000-00018]
 - 141 **Picozzi VJ**, Kozarek RA, Traverso LW. Interferon-based adjuvant chemoradiation therapy after pancreaticoduodenectomy for pancreatic adenocarcinoma. *Am J Surg* 2003; **185**: 476-480 [PMID: 12727570 DOI: 10.1016/S0002-9610(03)00051-5]
 - 142 **Hsu CC**, Herman JM, Corsini MM, Winter JM, Callister MD, Haddock MG, Cameron JL, Pawlik TM, Schulick RD, Wolfgang CL, Laheru DA, Farnell MB, Swartz MJ, Gunderson LL, Miller RC. Adjuvant chemoradiation for pancreatic adenocarcinoma: the Johns Hopkins Hospital-Mayo Clinic collaborative study. *Ann Surg Oncol* 2010; **17**: 981-990 [PMID: 20087786 DOI: 10.1245/s10434-009-0743-7]
 - 143 **Wayne JD**, Abdalla EK, Wolff RA, Crane CH, Pisters PW, Evans DB. Localized adenocarcinoma of the pancreas: the rationale for preoperative chemoradiation. *Oncologist* 2002; **7**: 34-45 [PMID: 11854545 DOI: 10.1634/theoncologist.7-1-34]
 - 144 **Moertel CG**, Frytak S, Hahn RG, O'Connell MJ, Reitemeier RJ, Rubin J, Schutt AJ, Weiland LH, Childs DS, Holbrook MA, Lavin PT, Livstone E, Spiro H, Knowlton A, Kalser M, Barkin J, Lessner H, Mann-Kaplan R, Ramming K, Douglas HO, Thomas P, Nave H, Bateman J, Lokich J, Brooks J, Chaffey J, Corson JM, Zamcheck N, Novak JW. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. *Cancer* 1981; **48**: 1705-1710 [PMID: 7284971]
 - 145 Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. Gastrointestinal Tumor Study Group. *J Natl Cancer Inst* 1988; **80**: 751-755 [PMID: 2898536]
 - 146 **Loehrer PJ**, Feng Y, Cardenes H, Wagner L, Brell JM, Cella D, Flynn P, Ramanathan RK, Crane CH, Alberts SR, Benson AB. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. *J Clin Oncol* 2011; **29**: 4105-4112 [PMID: 21969502 DOI: 10.1200/JCO.2011.34.8904]
 - 147 **Schellenberg D**, Kim J, Christman-Skieller C, Chun CL, Colombo LA, Ford JM, Fisher GA, Kunz PL, Van Dam J, Quon A, Desser TS, Norton J, Hsu A, Maxim PG, Xing L, Goodman KA, Chang DT, Koong AC. Single-fraction stereotactic body radiation therapy and sequential gemcitabine for the treatment of locally advanced pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2011; **81**: 181-188 [PMID: 21549517 DOI: 10.1016/j.ijrobp.2010.05.006]
 - 148 **Didolkar MS**, Coleman CW, Brenner MJ, Chu KU, Olexa N, Stanwyck E, Yu A, Neerchal N, Rabinowitz S. Image-guided stereotactic radiosurgery for locally advanced pancreatic adenocarcinoma results of first 85 patients. *J Gastrointest Surg* 2010; **14**: 1547-1559 [PMID: 20839073 DOI: 10.1007/s11605-010-1323-7]
 - 149 **Rwigema JC**, Heron DE, Parikh SD, Zeh HJ, Moser JA, Bahary N, Ashby K, Burton SA. Adjuvant stereotactic body radiotherapy for resected pancreatic adenocarcinoma with close or positive margins. *J Gastrointest Cancer* 2012; **43**: 70-76 [PMID: 20809393 DOI: 10.1007/S12029-010-9203-7]
 - 150 **Leibel SA**, Fuks Z, Zelefsky MJ, Hunt M, Burman CM, Mageras GS, Chui CS, Jackson A, Amols HI, Ling CC. Technological advances in external-beam radiation therapy for the treatment of localized prostate cancer. *Semin Oncol* 2003; **30**: 596-615 [PMID: 14571409]
 - 151 **Ling CC**, Burman C, Chui CS, Kutcher GJ, Leibel SA, LoSasso T, Mohan R, Bortfeld T, Reinstein L, Spirou S, Wang XH, Wu Q, Zelefsky M, Fuks Z. Conformal radiation treatment of prostate cancer using inversely-planned intensity-modulated photon beams produced with dynamic multileaf collimation. *Int J Radiat Oncol Biol Phys* 1996; **35**: 721-730 [PMID: 8690638 DOI: 10.1016/0360-3016(96)00174-5]
 - 152 **Varadarajulu S**, Trevino JM, Shen S, Jacob R. The use of endoscopic ultrasound-guided gold markers in image-guided radiation therapy of pancreatic cancers: a case series. *Endoscopy* 2010; **42**: 423-425 [PMID: 20232282 DOI: 10.1055/s-0029-1243989]
 - 153 **Villarreal MC**, Rajeshkumar NV, Garrido-Laguna I, De Jesus-Acosta A, Jones S, Maitra A, Hruban RH, Eshleman JR, Klein A, Laheru D, Donehower R, Hidalgo M. Personalizing cancer treatment in the age of global genomic analyses: PALB2 gene mutations and the response to DNA damaging agents in pancreatic cancer. *Mol Cancer Ther* 2011; **10**: 3-8 [PMID: 21135251 DOI: 10.1158/1535-7163.MCT-10-0893]
 - 154 **Yanagimoto H**, Shiomi H, Satoh S, Mine T, Toyokawa H, Yamamoto T, Tani T, Yamada A, Kwon AH, Komatsu N, Itoh K, Noguchi M. A phase II study of personalized peptide vaccination combined with gemcitabine for non-resectable pancreatic cancer patients. *Oncol Rep* 2010; **24**: 795-801 [PMID: 20664989]
 - 155 **Bapat AA**, Hostetter G, Von Hoff DD, Han H. Perineural invasion and associated pain in pancreatic cancer. *Nat Rev Cancer* 2011; **11**: 695-707 [PMID: 21941281 DOI: 10.1038/nrc3131]
 - 156 **Vincent A**, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. *Lancet* 2011; **378**: 607-620 [PMID: 21620466 DOI: 10.1016/S0140-6736(10)62307-0]
 - 157 **Kim EJ**, Simeone DM. Advances in pancreatic cancer. *Curr Opin Gastroenterol* 2011; **27**: 460-466 [PMID: 21778878 DOI: 10.1097/MOG.0b013e328349e31f]
 - 158 **Costello E**, Neoptolemos J. Enhancing the translation of cancer biomarkers. *Br J Surg* 2011; **98**: 1039-1040 [PMID: 21560125 DOI: 10.1002/bjs.7556]
 - 159 **Yachida S**, Jones S, Bozic I, Antal T, Leary R, Fu B, Kamiyama M, Hruban RH, Eshleman JR, Nowak MA, Velculescu VE, Kinzler KW, Vogelstein B, Iacobuzio-Donahue CA.

- Distant metastasis occurs late during the genetic evolution of pancreatic cancer. *Nature* 2010; **467**: 1114-1117 [PMID: 20981102 DOI: 10.1038/nature09515,]
- 160 **Collisson E**, Tempero M. Blinded by the light: molecular imaging in pancreatic adenocarcinoma. *Clin Cancer Res* 2011; **17**: 203-205 [PMID: 21106729 DOI: 10.1158/1078-0432]
 - 161 **Liang WS**, Craig DW, Carpten J, Borad MJ, Demeure MJ, Weiss GJ, Izatt T, Sinari S, Christoforides A, Aldrich J, Kurdoglu A, Barrett M, Phillips L, Benson H, Tembe W, Braggio E, Kiefer JA, Legendre C, Posner R, Hostetter GH, Baker A, Egan JB, Han H, Lake D, Stites EC, Ramanathan RK, Fonseca R, Stewart AK, Von Hoff D. Genome-wide characterization of pancreatic adenocarcinoma patients using next generation sequencing. *PLoS One* 2012; **7**: e43192 [PMID: 23071490 DOI: 10.1371/journal.pone.0043192]
 - 162 **Hermann PC**, Huber SL, Herrler T, Aicher A, Ellwart JW, Guba M, Bruns CJ, Heeschen C. Distinct populations of cancer stem cells determine tumor growth and metastatic activity in human pancreatic cancer. *Cell Stem Cell* 2007; **1**: 313-323 [PMID: 18371365 DOI: 10.1016/j.stem.2007.06.002]
 - 163 **Li C**, Heidt DG, Dalerba P, Burant CF, Zhang L, Adsay V, Wicha M, Clarke MF, Simeone DM. Identification of pancreatic cancer stem cells. *Cancer Res* 2007; **67**: 1030-1037 [PMID: 17283135 DOI: 10.1158/0008-5472.CAN-06-2030]
 - 164 **Penchev VR**, Rasheed ZA, Maitra A, Matsui W. Heterogeneity and targeting of pancreatic cancer stem cells. *Clin Cancer Res* 2012; **18**: 4277-4284 [PMID: 22896694 DOI: 10.1158/1078-0432.CCR-11-3112]
 - 165 **Rhim AD**, Mirek ET, Aiello NM, Maitra A, Bailey JM, McAllister F, Reichert M, Beatty GL, Rustgi AK, Vonderheide RH, Leach SD, Stanger BZ. EMT and dissemination precede pancreatic tumor formation. *Cell* 2012; **148**: 349-361 [PMID: 22265420 DOI: 10.1016/j.cell.2011.11.025]
 - 166 **Jimeno A**, Feldmann G, Suárez-Gauthier A, Rasheed Z, Solomon A, Zou GM, Rubio-Viqueira B, García-García E, López-Ríos F, Matsui W, Maitra A, Hidalgo M. A direct pancreatic cancer xenograft model as a platform for cancer stem cell therapeutic development. *Mol Cancer Ther* 2009; **8**: 310-314 [PMID: 19174553 DOI: 10.1158/1535-7163.MCT-08-924]
 - 167 **Rajeshkumar NV**, Rasheed ZA, García-García E, López-Ríos F, Fujiwara K, Matsui WH, Hidalgo M. A combination of DR5 agonistic monoclonal antibody with gemcitabine targets pancreatic cancer stem cells and results in long-term disease control in human pancreatic cancer model. *Mol Cancer Ther* 2010; **9**: 2582-2592 [PMID: 20660600 DOI: 10.1158/1535-7163.mCT-10-0370]
 - 168 **Zhang GN**, Liang Y, Zhou LJ, Chen SP, Chen G, Zhang TP, Kang T, Zhao YP. Combination of salinomycin and gemcitabine eliminates pancreatic cancer cells. *Cancer Lett* 2011; **313**: 137-144 [PMID: 22030254 DOI: 10.1016/j.canlet.2011.05.030]
 - 169 **Mahadevan D**, Von Hoff DD. Tumor-stroma interactions in pancreatic ductal adenocarcinoma. *Mol Cancer Ther* 2007; **6**: 1186-1197 [PMID: 17406031 DOI: 10.1158/1535-7163.MCT-06-0686]
 - 170 **Masamune A**, Shimosegawa T. Signal transduction in pancreatic stellate cells. *J Gastroenterol* 2009; **44**: 249-260 [PMID: 19271115 DOI: 10.1007/s00535-009-0013-2]
 - 171 **Erkan M**, Reiser-Erkan C, Michalski CW, Deucker S, Sauiunaite D, Streit S, Esposito I, Friess H, Kleeff J. Cancer-stellate cell interactions perpetuate the hypoxia-fibrosis cycle in pancreatic ductal adenocarcinoma. *Neoplasia* 2009; **11**: 497-508 [PMID: 19412434]
 - 172 **Jacobetz MA**, Chan DS, Neesse A, Bapiro TE, Cook N, Frese KK, Feig C, Nakagawa T, Caldwell ME, Zecchini HI, Lolkema MP, Jiang P, Kultti A, Thompson CB, Maneval DC, Jodrell DJ, Frost GL, Shepard HM, Skepper JN, Tuveson DA. Hyaluronan impairs vascular function and drug delivery in a mouse model of pancreatic cancer. *Gut* 2013; **62**: 112-120 [PMID: 22466618 DOI: 10.1136/gutjnl-2012-302529]
 - 173 **Beatty GL**, Chiorean EG, Fishman MP, Saboury B, Teitelbaum UR, Sun W, Huhn RD, Song W, Li D, Sharp LL, Torigian DA, O'Dwyer PJ, Vonderheide RH. CD40 agonists alter tumor stroma and show efficacy against pancreatic carcinoma in mice and humans. *Science* 2011; **331**: 1612-1616 [PMID: 21436454 DOI: 10.1126/science.1198443]
 - 174 **Schrader H**, Wiese M, Ellrichmann M, Belyaev O, Uhl W, Tannapfel A, Schmidt W, Meier J. Diagnostic value of quantitative EUS elastography for malignant pancreatic tumors: relationship with pancreatic fibrosis. *Ultraschall Med* 2012; **33**: E196-E201 [PMID: 21630184 DOI: 10.1055/s-0031-1273256]
 - 175 **Von Hoff DD**, Korn R, Mousses S. Pancreatic cancer--could it be that simple? A different context of vulnerability. *Cancer Cell* 2009; **16**: 7-8 [PMID: 19573807 DOI: 10.1016/j.ccr.2009.06.011]
 - 176 **Le A**, Rajeshkumar NV, Maitra A, Dang CV. Conceptual framework for cutting the pancreatic cancer fuel supply. *Clin Cancer Res* 2012; **18**: 4285-4290 [PMID: 22896695 DOI: 10.1158/1078-0432.CCR-12-0041]
 - 177 **Li D**, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL. Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology* 2009; **137**: 482-488 [PMID: 19375425 DOI: 10.1053/j.gastro.2009.04.013]
 - 178 **Kisfalvi K**, Eibl G, Sinnott-Smith J, Rozengurt E. Metformin disrupts crosstalk between G protein-coupled receptor and insulin receptor signaling systems and inhibits pancreatic cancer growth. *Cancer Res* 2009; **69**: 6539-6545 [PMID: 19679549 DOI: 10.1158/0008-5472.CAN-09-0418]
 - 179 **Ma WW**, Jacene H, Song D, Vilardell F, Messersmith WA, Laheru D, Wahl R, Endres C, Jimeno A, Pomper MG, Hidalgo M. [18F]fluorodeoxyglucose positron emission tomography correlates with Akt pathway activity but is not predictive of clinical outcome during mTOR inhibitor therapy. *J Clin Oncol* 2009; **27**: 2697-2704 [PMID: 19380450 DOI: 10.1200/JCO.2008.18.8383]
 - 180 **Garrido-Laguna I**, Tan AC, Uson M, Angenendt M, Ma WW, Villaroel MC, Zhao M, Rajeshkumar NV, Jimeno A, Donehower R, Iacobuzio-Donahue C, Barrett M, Rudek MA, Rubio-Viqueira B, Laheru D, Hidalgo M. Integrated preclinical and clinical development of mTOR inhibitors in pancreatic cancer. *Br J Cancer* 2010; **103**: 649-655 [PMID: 20664591 DOI: 10.1038/sj.bjc.6605819]
 - 181 **Guo JY**, Chen HY, Mathew R, Fan J, Strohecker AM, Karsli-Uzunbas G, Kamphorst JJ, Chen G, Lemons JM, Karantz V, Collier HA, Dipaola RS, Gelinas C, Rabinowitz JD, White E. Activated Ras requires autophagy to maintain oxidative metabolism and tumorigenesis. *Genes Dev* 2011; **25**: 460-470 [PMID: 21317241 DOI: 10.1101/gad.2016311]

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650 0 a| Medicine, Experimental v| Periodicals.

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Appendix SASAKI02

Improvement of Treatment Outcomes for Metastatic Pancreatic Cancer: A Real-world Data Analysis

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MASATO MATSUYAMA, MASATO OZAKA and NAOKI SASAHIRA

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Foundation of Cancer Research, Tokyo, Japan*

Abstract. *Background/Aim:* FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, oxaliplatin) and gemcitabine plus nab-paclitaxel therapy have recently been introduced for the treatment of metastatic pancreatic cancer. Herein, overall treatment outcomes of metastatic pancreatic cancer after introduction of FOLFIRINOX and gemcitabine plus nab-paclitaxel therapy were evaluated, in daily practice. *Patients and Methods:* Metastatic pancreatic cancer patients (n=321) who started systemic chemotherapy between January 2011 and December 2016 were included and were divided into two groups: group A (2011-2013) and group B (2014-2016). Treatment outcomes were evaluated retrospectively. *Results:* Patient characteristics were similar between the two groups except for the rates of distant lymph node metastasis and peritoneal metastasis. The preferred regimens in groups A and B were gemcitabine monotherapy and gemcitabine plus nab-paclitaxel therapy, respectively. The response rates, median progression-free survival, and median overall survival of groups A and B were 7.8% and 28.4% ($p<0.01$), 3.1 months and 5.4 months ($p<0.01$), and 6.7 months and 10.2 months ($p<0.01$), respectively. *Conclusion:* Overall treatment outcomes for metastatic pancreatic cancer were significantly improved after introduction of FOLFIRINOX and gemcitabine plus nab-paclitaxel combination therapy in daily practice.

Pancreatic cancer is the fourth leading cause of cancer-related deaths, since more than 33,000 patients are dying from this type of cancer annually in Japan (1). The prognosis of

pancreatic cancer remains dismal, and the mortality rates closely follow the incidence rates. Surgical resection with negative margins (R0) is the only potentially curative treatment for pancreatic cancer, but only 15-20% of these patients are eligible for resection at initial diagnosis (2). More than half of patients diagnosed in the metastatic setting have a 5-year survival rate of 2.6% (2).

Gemcitabine alone has since long been the standard chemotherapy for metastatic pancreatic cancer (3). Many randomized studies have been conducted to develop regimens that are more effective than gemcitabine alone. Combination therapy with gemcitabine and erlotinib demonstrated a significant improvement in prognosis against gemcitabine alone, but the improvement of median overall survival was only two weeks (4). Recently, combination therapy including FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, oxaliplatin) and gemcitabine plus nab-paclitaxel therapy (GEM+nab-PTX) showed superiority to gemcitabine alone (5, 6). Both these regimens are combination therapies of cytotoxic agents. The prognoses were prolonged by 4.3 months by FOLFIRINOX and 1.8 months by GEM+nab-PTX. Although it is difficult to compare these results directly because the study populations in each trial were different, these two regimens have become the two standard front-line treatments for metastatic pancreatic cancer.

Unfortunately, FOLFIRINOX and GEM+nab-PTX are more toxic than is gemcitabine alone (5, 6). To reduce the severe adverse events of FOLFIRINOX, several modified regimens have been tested and reported. In a phase II study, a modified version of FOLFIRINOX with a reduced dose of irinotecan to 150 mg/m² and without the bolus of 5-fluorouracil, demonstrated a similar efficacy and reduced toxicity to FOLFIRINOX in Japanese pancreatic cancer patients (7). This modified regimen is widely used in daily practice in Japan, but this regimen remains more toxic than gemcitabine alone. Moreover, pancreatic cancer is generally a disease of the elderly, with a median age of diagnosis at 70 years, even though 40% are older than 75 years when diagnosed (8). In Japan, the median age of pancreatic cancer

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Key Words: Metastatic pancreatic cancer, chemotherapy, FOLFIRINOX, gemcitabine, nab-paclitaxel, real-world data.

Table I. Patient characteristics.

	Group A (n=102)	Group B (n=201)	p-Value
Age (median, range)	66 (37-80)	66 (39-82)	0.80
Gender			0.63
Male	58 (57%)	107 (53%)	
Female	44 (43%)	94 (47%)	
Performance status			0.37
0	82 (80%)	147 (73%)	
1	19 (19%)	51 (25%)	
2	1 (1%)	3 (1%)	
Primary site			0.38
Pancreatic head	33 (32%)	76 (38%)	
Pancreatic body-tail	69 (68%)	125 (62%)	
Metastatic site			
Liver metastasis	74 (73%)	149 (74%)	0.78
Lung metastasis	15 (15%)	32 (16%)	0.87
Distant lymph node metastasis	41 (40%)	51 (25%)	0.01
Peritoneal metastasis	36 (35%)	39 (19%)	<0.01
CEA (ng/ml)	5.9 (0.7-4,924)	6.4 (0-9,698.9)	0.66
CA19-9 (U/ml)	1,153.5 (2-50,000)	1,727 (2-50,000)	0.89
Biliary drainage	21 (21%)	42 (21%)	1.00

CEA, Carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

diagnosis is now 75 years due to the high life expectancy (1). Furthermore, there are many metastatic pancreatic cancer patients with a poor performance status (8). Consequently, these two combination therapies could be used in selected metastatic pancreatic cancer patients who maintained good performance status, while the remaining ones are still treated with gemcitabine alone. In the present study, we conducted a retrospective analysis to evaluate the improvement in treatment outcomes for metastatic pancreatic cancer patients after introduction of FOLFIRINOX and GEM+nab-PTX in their daily practice.

Patients and Methods

Patients. Patients with primary metastatic pancreatic cancer who started systemic chemotherapy between January 2011 and December 2016 at our hospital were included in this retrospective study. The patients who were recurrent after surgery were excluded from this study. In Japan, FOLFIRINOX and GEM+nab-PTX became commercially available in December 2013 and December 2014, respectively. FOLFIRINOX was first introduced at our hospital in January 2014. Therefore, the study population was divided into two groups: patients who started chemotherapy between 2011 and 2013 were as assigned to group A, and patients who started chemotherapy between 2014 and 2016 were as assigned to group B. Several clinical studies evaluating new agents as first-line chemotherapy were conducted during this period, and the patients who were included in these clinical studies were excluded from this study population. Clinical study regimens as second-line chemotherapy were allowed in this study when the patients were progressed after first-line standard chemotherapy. For FOLFIRINOX, all patients

were treated with modified regimens (7) during these periods as both first-line and second-line chemotherapy.

Statistical analysis. Objective response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (9). Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier method, and the log-rank test for comparisons between two groups. Hazard ratio (HR) and 95% confidence intervals were estimated by the Cox proportional hazard model. The Mann-Whitney *U*- and Fisher's exact tests were used to compare the two groups as appropriate. The final analysis was conducted using follow-up data through the end of May 2018. Multivariate analysis was conducted to evaluate prognostic factors of metastatic pancreatic cancer by using a Cox proportional hazard model. JMP 12 statistical software (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

This study was conducted in compliance with the Declaration of Helsinki and according to the ethical guidelines for medical and health research involving human subjects. This study was approved by the Institutional Review Boards of our hospital (No. 2017-1140).

Results

Patient characteristics. A total of 321 consecutive patients with primary metastatic pancreatic cancer were treated with systemic chemotherapy between January 2011 and December 2016, out of which 18 were treated by a clinical study regimen. Therefore, a total of 303 patients were enrolled in this study. Pathological confirmation was achieved in 97.0% of the patients (294/303; 284 adenocarcinoma, 1 adenosquamous cell carcinoma, 8

Table II. Treatment regimens.

	Group A (n=102)	Group B (n=201)
Gemcitabine	83 (81.3%)	38 (18.9%)
S-1	11 (10.8%)	9 (4.5%)
Gemcitabine+S-1	2 (2.0%)	3 (1.5%)
Gemcitabine+erlotinib	6 (5.9%)	0
Gemcitabine+nab-paclitaxel	0	122 (60.7%)
Modified FOLFIRINOX	0	29 (14.4%)

carcinoma, and 1 class IV by cytology). The remaining 9 patients (3.0%), who did not have pathological evidence, were diagnosed with metastatic pancreatic cancer through the clinical course. Patient characteristics are shown in Table I. One hundred and two patients were enrolled in group A (2011-2013) and 201 patients were in group B (2014-2016). The baseline characteristics were well balanced between these two groups except for the rates of distant lymph node metastasis and peritoneal metastasis. The median age of both A and B group was 66 years. Most patients demonstrated relatively a good performance status. Treatment regimens are summarized in Table II. Gemcitabine monotherapy was the most frequently selected regimen in group A, while GEM+nab-PTX was the most frequently selected therapy used in group B. In the latter, approximately three-quarters of the patients were treated by modified FOLFIRINOX or GEM+nab-PTX. Gemcitabine and tegafur/gimeracil/oteracil potassium (S-1) combination therapy was only used in limited populations in both groups due to the results of the GEST study (10).

Treatment outcomes. The median follow-up period after treatment was 8.6 months. All final survival data were confirmed in group A. In group B, 19 patients (9.5%) were still alive when the data were analyzed, while for 3 patients lacked final survival data (1.5%).

Treatment outcomes are summarized in Table III. Response rates of groups A and B to treatment were 7.8% and 28.4%, respectively ($p<0.01$). Disease control rates in groups A and B were 53.9% and 65.7%, respectively ($p=0.06$). Median PFS periods in groups A and B were 3.1 months and 5.4 months, respectively ($p<0.01$; Figure 1). Median OS periods in groups A and B were 6.7 months and 10.2 months, respectively ($p<0.01$; Figure 2). One- and 2-year survival rates in group B improved to 42.0% and 13.9% when compared to those in group A, respectively. Induction rates of second-line chemotherapy in groups A and B were 51.6% and 65.4%, respectively ($p=0.04$). In group A, 80.9% of patients were treated with S-1 monotherapy and 8.5% were treated with gemcitabine monotherapy. Only 1 patient

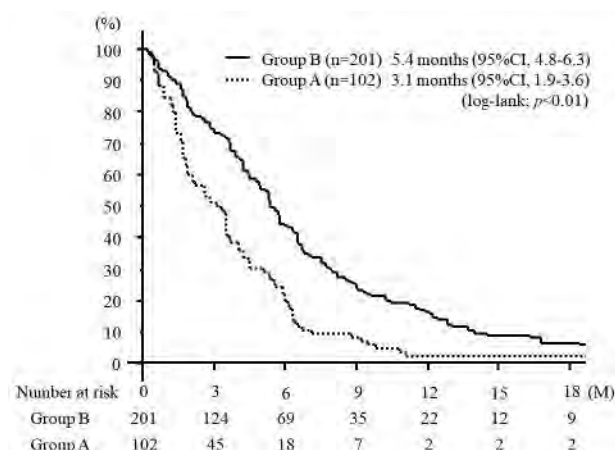


Figure 1. Progression-free survival of group A and B. 95%CI, 95% Confidence interval; M, months.

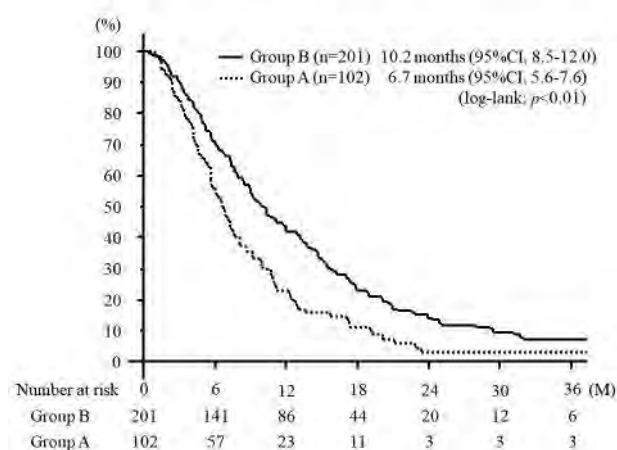


Figure 2. Overall survival of group A and B. 95%CI, 95% Confidence interval; M, months.

(2.1%) was treated with GEM+nab-PTX, and no patient was treated with modified FOLFIRINOX in group A. In group B, 48.0% of the patients were treated with S-1 monotherapy, and modified FOLFIRINOX was selected in 26.0% of the patients. GEM+nab-PTX and gemcitabine monotherapy were chosen in 13.0% and 6.0% of patients, respectively in group B, while 6 patients (3.0%) were offered surgical resection after first-line chemotherapy (two patients (2/29; 6.9%) with modified FOLFIRINOX, and the remaining 4 patients (4/122; 3.3%) were treated with GEM+nab-PTX). The median follow-up time in 6 resected patients was 36.0 months, and 5/6 patients were still alive at the time of study. No patients from group A were allowed to undergo surgical resection.

Table III. Summary of treatment outcomes.

	Group A (n=102)	Group B (n=201)	p-Value
Response rate	7.8%	28.4%	<0.01
Disease control rate	53.9%	65.7%	0.06
Progression-free survival (months)	3.1	5.4	<0.01
6-month progression-free survival rate	19.8%	43.7%	
1-year progression-free survival rate	2.3%	16.2%	
Induction rate of second-line chemotherapy	51.6%	65.4%	0.04
Overall survival (months)	6.7	10.2	<0.01
1-year survival rate	22.6%	42.0%	
2-years survival rate	2.9%	13.9%	

Table IV. Prognostic factors of chemotherapy for metastatic pancreatic cancer.

Variables	Univariate		Multivariate	
	HR (95%CI)	p-Value	HR (95%CI)	p-Value
Age (≥ 70 years)	1.14 (0.89-1.45)	0.29		
Sex (male)	1.06 (0.84-1.34)	0.62		
Performance status (0, 1)	0.19 (0.08-0.63)	0.01	0.25 (0.10-0.83)	0.03
Primary site (pancreatic head)	1.09 (0.85-1.39)	0.49		
Liver metastasis	1.80 (1.37-2.37)	<0.01	1.97 (1.46-2.67)	<0.01
Lung metastasis	1.02 (0.73-1.39)	0.91		
Distant lymph node metastasis	1.20 (0.92-1.54)	0.17		
Peritoneal metastasis	1.35 (1.02-1.76)	0.03	1.56 (1.16-2.08)	<0.01
CEA	1.04 (0.17-3.30)	0.96		
CA19-9	1.62 (1.17-2.21)	<0.01	1.47 (1.05-2.03)	0.03
Biliary drainage	1.24 (0.92-1.64)	0.16		
GEM+nab-PTX or mFOLFIRINOX	0.50 (0.39-0.64)	<0.01	0.51 (0.40-0.65)	<0.01

CEA, Carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; GEM+nab-PTX, gemcitabine+nab-paclitaxel; mFOLFIRINOX, modified FOLFIRINOX; HR, hazard ratio; 95%CI, 95% confidence interval.

In group B, the response rate, disease control rate, median PFS and OS of patients treated with modified FOLFIRINOX were 41.4%, 72.4%, 7.0 months and 17.1 months, respectively. The response rate, disease control rate, median PFS and OS of patients treated with GEM+nab-PTX were 33.6%, 74.6%, 5.7 months and 11.5 months, respectively. The response rate, disease control rate, median PFS and OS of patients treated with the other regimens in group B were 8.0%, 40%, 2.8 months and 5.7 months, respectively.

Multivariate analysis for prognostic factors. The results of our multivariate analysis are shown in Table IV. Good performance status (HR=0.25) and introduction of modified FOLFIRINOX or GEM+nab-PTX as first-line chemotherapy (HR=0.51) emerged as better prognostic factors for

metastatic pancreatic cancer. High levels of carbohydrate antigen 19-9 (CA19-9) (HR=1.47), the presence of liver metastasis (HR=1.97) and peritoneal metastasis (HR=1.56) emerged as poor prognostic factors.

Discussion

The overall treatment outcomes of metastatic pancreatic cancer have improved in the clinical setting due to the introduction of FOLFIRINOX and GEM+nab-PTX. More than 75% of the metastatic pancreatic cancer patients we studied were treated with modified FOLFIRINOX or GEM+nab-PTX in group B (2014-2016). In this group, tumor shrinkage was achieved more frequently compared to group A (3.6 times; 28.4% vs. 7.8%) and similarly, PFS was prolonged to 5.4 months, achieving a 2.3-month extension. Median OS was prolonged

from 6.7 months to 10.2 months and the 1-year survival rate was 42.0%. Approximately 14% of metastatic pancreatic cancer patients in group B survived for more than 2 years.

Because of the better efficacies of modified FOLFIRINOX and GEM+nab-PTX, 6 patients (3.0%) in group B had surgical resection. In the era before FOLFIRINOX and GEM+nab-PTX, it was extremely rare that patients with metastatic pancreatic cancer would undergo surgical resection (11). The median follow-up time of 6 resected patients was 36.0 months, and 5/6 patients were still alive. Although a long-term follow up is necessary to validate the efficacy of conversion surgery for metastatic pancreatic cancer, the introduction of efficacious chemotherapeutic regimens is undoubtedly a great opportunity that allows conversion surgery in these patients. The major criteria of conversion surgery in our hospital are: i) disappearance of metastatic lesions; ii) resectable primary lesion; iii) normalization of tumor markers; and iv) duration of chemotherapy for at least eight months. The last criterion was chosen based on data from a study conducted by the Japanese Society of Hepato-Biliary-Pancreatic Surgery (11). We believe that the criteria for conversion surgery need to be stricter for metastatic pancreatic cancer than for locally advanced pancreatic cancer, thus chemotherapy was sometimes extended for 1 year. Therefore, only a stringent group of selected patients underwent surgical resection even after the introduction of FOLFIRINOX and GEM+nab-PTX.

Improvements in median PFS and OS between groups A and B were 2.3 months and 3.5 months, respectively. The difference between the PFS and OS was only 1.2 months, suggesting that the impact of second-line chemotherapy remained limited, even in group B (2014-2016). The most widely used second-line chemotherapy in group B was S-1 monotherapy (48.0%), while treatment with modified FOLFIRINOX (26.0%) was second best. Even in the modified regimen of FOLFIRINOX, only a few patients were able to benefit from it. Therefore, a less toxic yet effective second-line chemotherapy is needed. Nanoliposomal irinotecan with fluorouracil and folinic acid might be a good option for patients having second-line chemotherapy (12). Quite importantly, an effective third-line chemotherapy should be available to prolong the OS of metastatic pancreatic cancer patients.

There was a trend towards improvement in the disease control rate of group B, but it was not statistically significant compared to group A ($p=0.06$). The disease control rate in group B was only 65.7%. Many patients in this group were diagnosed at extremely advanced stages and could not continue the treatment long enough even if first-line chemotherapy had already been introduced. Early diagnosis is essential to resolve this problem, and educational activities for citizens regarding pancreatic cancer are still needed. Moreover, the median age of diagnosing pancreatic cancer

in Japan is now 75 years because of high life expectancy (1). Approximately 33% of the pancreatic cancer patients were older than 80 years of age when diagnosed in Japan (1). More than 20% of the patients in group B chose monotherapy even though treatment with GEM+nab-PTX is relatively tolerable. Therefore, some new less toxic regimens are required to resolve this problem. It is also very important to establish standard treatment for elderly patients with metastatic pancreatic cancer (13-14).

Limitations of this study include that the data were collected from a single cancer center and were retrospectively analyzed. There were several treatment regimens involved in this study, and it is difficult to compare the adverse events. Therefore, it is not clear whether prolonging the survival time was concomitant with maintaining a good quality of life. There is a possibility that quality of life deteriorated due to the adverse events of FOLFIRINOX or GEM+nab-PTX, as it has been reported previously (14). Peripheral neurotoxicity is now a substantial problem in the management of pancreatic cancer patients who are treated with these chemotherapies (5, 6, 15). It is important to establish the management of this side-effect and to develop new effective chemotherapies with different profiles of adverse events (16-20).

In conclusion, overall treatment outcomes of chemotherapy for metastatic pancreatic cancer were significantly improved after introduction of FOLFIRINOX and GEM+nab-PTX in the daily practice. However, about 25% of the metastatic pancreatic cancer patients could not be treated with these two effective regimens as first-line chemotherapy. Furthermore, only less than 40% of the patients were treated with these two regimens as second-line chemotherapy. More effective second-line and third-line chemotherapy regimens with less toxicity are required to prolong the overall survival of metastatic pancreatic cancer patients.

References

- 1 Cancer Registry and Statistics: Cancer Information Service, National Cancer Center, Japan. 2018. https://ganjoho.jp/reg_stat/statistics/dl/index.html. Accessed October 2018.
- 2 Ilic M and Ilic I: Epidemiology of pancreatic cancer. *World J Gastroenterol* 22: 9694-9705, 2016.
- 3 Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD and Von Hoff DD: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 15: 2403-2413, 1997.
- 4 Moore MJ, Goldstein D, Hamm J, Figier A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, Campos D, Lim R, Ding K, Clark G, Voskoglou-Nomikos T, Ptasynski M, Parulekar W; National Cancer Institute of Canada Clinical Trials Group: Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 25: 1960-1966, 2007.

- 5 Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécauarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardiére C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 364: 1817-1825, 2011.
- 6 Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J and Renschler MF: Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 369: 1691-1703, 2013.
- 7 Ozaka M, Ishii H, Sato T, Ueno M, Ikeda M, Uesugi K, Sata N, Miyashita K, Mizuno N, Tsuji K, Okusaka T and Furuse J: A phase II study of modified FOLFIRINOX for chemotherapy-naïve patients with metastatic pancreatic cancer. *Cancer Chemother Pharmacol* 81: 1017-1023, 2018.
- 8 Sohal DP, Mangu PB, Khorana AA, Shah MA, Philip PA, O'Reilly EM, Uronis HE, Ramanathan RK, Crane CH, Engebretson A, Ruggiero JT, Copur MS, Lau M, Urba S and Laheru D: Metastatic pancreatic cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 34: 2784-2796, 2016.
- 9 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D and Verweij J: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 45: 228-247, 2009.
- 10 Ueno H, Ioka T, Ikeda M, Ohkawa S, Yanagimoto H, Boku N, Fukutomi A, Sugimori K, Baba H, Yamao K, Shimamura T, Sho M, Kitano M, Cheng AL, Mizumoto K, Chen JS, Furuse J, Funakoshi A, Hatori T, Yamaguchi T, Egawa S, Sato A, Ohashi Y, Okusaka T and Tanaka M: Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. *J Clin Oncol* 31: 1640-1648, 2013.
- 11 Satoi S, Yamaue H, Kato K, Takahashi S, Hirono S, Takeda S, Eguchi H, Sho M, Wada K, Shintchi H, Kwon AH, Hirano S, Kinoshita T, Nakao A, Nagano H, Nakajima Y, Sano K, Miyazaki M and Takada T: Role of adjuvant surgery for patient with initially unresectable pancreatic cancer with a long-term favorable response to non-surgical anti-cancer treatments: results of a project study for pancreatic surgery by the Japanese Society of Hepato-Biliary-Pancreatic Surgery. *J Hepatobiliary Pancreat Sci* 20: 590-600, 2013.
- 12 Wang-Gillam A, Li CP, Bodoky G, Dean A, Shan YS, Jameson G, Macarulla T, Lee KH, Cunningham D, Blanc JF, Hubner RA, Chiu CF, Schwartzmann G, Siveke JT, Braiteh F, Moyo V, Belanger B, Dhindsa N, Bayever E, Von Hoff DD, Chen LT; NAPOLI-1 Study Group: Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomized, open-label, phase 3 trial. *Lancet* 387: 545-557, 2016.
- 13 Ishii H, Yamashita N, Ueno M, Ohkawa S, Saito AM and Sekimoto M: A randomized controlled trial of gemcitabine hydrochloride plus S-1 combination therapy versus gemcitabine hydrochloride therapy alone in pancreatic cancer patients aged ≥ 75 years: a study protocol for an open-label randomized feasibility study. *BMJ Open Gastroenterol* 5: e000187, 2018.
- 14 Betge J, Chi-Kern J, Schulte N, Belle S, Gutting T, Burgermeister E, Jesenofsky R, Maenz M, Wedding U and Ebert MP, N: A multicenter phase 4 geriatric assessment directed trial to evaluate gemcitabine +/- nab-paclitaxel in elderly pancreatic cancer patients (GrantPax). *BMC Cancer* 18: 747, 2018.
- 15 Goldstein D, Von Hoff DD, Moore M, Greeno E, Tortora G, Ramanathan RK, Macarulla T, Liu H, Pilot R, Ferrara S and Lu B: Development of peripheral neuropathy and its association with survival during treatment with nab-paclitaxel plus gemcitabine for patients with metastatic adenocarcinoma of the pancreas: A subset analysis from a randomized phase III trial (MPACT). *Eur J Cancer* 52: 85-91, 2016.
- 16 Ma J, Kavelaars A, Dougherty PM and Heijnen CJ: Beyond symptomatic relief for chemotherapy-induced peripheral neuropathy: Targeting the source. *Cancer* 124: 2289-2298, 2018.
- 17 Smith EM, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, Bressler LR, Fadul CE, Knox C, Le-Lindqwister N, Gilman PB, Shapiro CL; Alliance for Clinical Trials in Oncology: Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. *JAMA* 309: 1359-1367, 2013.
- 18 Scheithauer W, Ramanathan RK, Moore M, Macarulla T, Goldstein D, Hammel P, Kunzmann V, Liu H, McGovern D, Romano A and Von Hoff DD: Does modification and efficacy of nab-paclitaxel plus gemcitabine vs. gemcitabine for patients with metastatic pancreatic cancer: phase III MPACT trial. *J Gastrointest Oncol* 7: 469-478, 2016.
- 19 Relias V, Maloney A, Smith MH and Saif MW: Does "OPTINAB" strategy ("stop-and-go") work in treatment of advanced pancreatic cancer (APC) with nab-paclitaxel-gemcitabine? *Cancer Chemother Pharmacol* 80: 371-375, 2017.
- 20 Tong H, Fan Z, Liu B and Lu T: The benefits of modified FOLFIRINOX for advanced pancreatic cancer and its induced adverse events: a systematic review and meta-analysis. *Sci Rep* 8: 8666, 2018.

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Appendix SCHOBBER01

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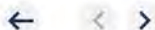

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Appendix SCHOBBER02

New Advances in the Treatment of Metastatic Pancreatic Cancer

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Key Words

Chemotherapy · Pancreatic ductal adenocarcinoma · FOLFIRINOX · Nab-paclitaxel · Chemoresistance

Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is characterised by an extremely poor overall survival (OS) compared to other solid tumours. As the incidence of the disease is rising and the treatment options are limited, PDAC is projected to be the 2nd leading cause of cancer-related deaths in the United States by 2030. A majority of patients are not eligible for curative resection at the time of diagnosis, and those that are resected will often relapse within the first few years after surgery. **Summary:** Until recently, the nucleoside analogue gemcitabine has been the standard of care for patients with non-resectable PDAC with only marginal effects on OS. In 2011, the gemcitabine-free FOLFIRINOX regimen (folinic acid, fluorouracil, irinotecan and oxaliplatin) showed a significant survival advantage for patients with metastatic PDAC in a phase III trial. In 2013, the Metastatic Pancreatic Adenocarcinoma Trial phase III trial with nano-

formulated albumin-bound paclitaxel (nab-paclitaxel) in combination with gemcitabine also resulted in a significant survival extension compared to gemcitabine monotherapy. However, both intensified therapy regimens show a broad spectrum of side effects and patients need to be carefully selected for the most appropriate protocol. **Key Message:** In this study, recent advances in the chemotherapeutic options available to treat metastatic PDAC and their implications for today's treatment choices are reviewed.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is considered to be one of the most lethal solid organ tumour. The extraordinarily poor prognosis can be attributed to the lack of early clinical symptoms and good biomarkers, early metastatic dissemination and an unusually high resistance to targeted and cytotoxic agents. The incidence of pancreatic cancer ranges worldwide from 1 to 10 cases per 100,000, out of which 85% are adenocarcinomas [1]. The

Table 1. Currently recruiting and ongoing clinical phase III trials with intensive chemotherapy

Design	Compound/specifics	Clinical trial
Adjuvant		
Gemcitabine + nab vs. gemcitabine		NCT01964430
Gemcitabine vs. FOLFIRINOX		NCT02355119
Gemcitabine vs. mFOLFIRINOX		NCT01526135
Neoadjuvant		
Surgery + gemcitabine adjuvant vs. FOLFIRINOX neoadjuvant – surgery – FOLFIRINOX adjuvant		NCT02172976
Surgery + PEXG adjuvant vs. PEXG neoadjuvant + surgery + adjuvant vs. gemcitabine adjuvant		NCT01150630
Palliative 1st-line		
Gemcitabine vs. FOLFOX	hENT1 expression	NCT01586611
Gemcitabine + nab + ibrutinib vs. gemcitabine + nab	Bruton's tyrosine kinase inhibitor	NCT02436668

incidence is slightly higher in developed countries, among men, and a number of risk factors as well as genetic syndromes/mutations that are associated with pancreatic cancer have been identified [1, 2]. The genetic hallmark of PDAC is an activating KRAS mutation, followed by the deletion or the inactivation of mutations in tumour-suppressor genes such as p16, DPC4 and p53 [3–5]. Extensive experimental studies in mice and men have identified and characterised a molecular and histological progression model ranging from early to advanced precursor lesions (so called pancreatic intraepithelial neoplasia lesions, PanIN I–III), to frank adenocarcinoma. Moreover, PDAC is typically accompanied by an extensive desmoplastic stroma reaction contributing to a hypovascular and hypoxic microenvironment, which possibly affects the delivery and efficacy of chemotherapeutic agents, reprogramming of cellular metabolism and evasion of tumour immunity [6–8].

Clinical symptoms of PDAC patients are often very unspecific and hard to detect early. Patients may complain of abdominal discomfort (with no signs of peritoneal irritation), weight loss, painless jaundice and unspecific back pain [9, 10]. Onset of type II diabetes as well as unexplained deep vein thrombosis may also indicate the development of PDAC, but also occur for many other reasons in the elderly. Once the diagnosis of PDAC is suspected, a multi-modal diagnostic work-up using modalities such as sonography, endosonography, multi-slice CT as well as MRI should be performed in a multi-disciplinary team. In case of a metastatic disease, histological confirmation prior to cytotoxic treatment is obligatory. Surgical resection is the only potentially curative treatment and criteria of surgical resectability are based on

the involvement of the local vessels [11] and presence or absence of metastatic disease. Until now, only about 20–25% of patients are eligible for surgical resection. Current treatment standards advocate the use of adjuvant chemotherapy following surgery. For locally advanced pancreatic adenocarcinoma (LAPC), there is growing interest in the use of neoadjuvant approaches, which are being evaluated, as in the currently recruiting Conko 007 trial (EUDRACT Nr. 2009-014476-21). This phase III trial is evaluating the role of a combined chemoradiotherapy after leading-in with chemotherapy in patients with LAPC, interestingly already making use of FOLFIRINOX as a potential treatment arm. The currently enrolling NEONAX-trial, a phase II trial conducted by the AIO (EUDRACT-Nr. 2013-005559-34), is addressing the question of whether or not a neoadjuvant combination treatment with nab-paclitaxel and gemcitabine plus adjuvant or only adjuvant gemcitabine and nab-paclitaxel treatment can downstage the tumour prior to surgery in patients with resectable PDAC (table 1). Despite numerous clinical trials in stage IV (metastatic) PDAC, there has only been a modest improvement of median survival rates for this group of patients [12–15]. In the last 2 decades, biomarker discovery and validation has been a key area of research to stratify patients, predict response to treatment and enable the development of a tailored treatment approach. The aim of this review is to provide a comprehensive overview of the development of chemotherapeutic regimens that have been used for the treatment of metastatic PDAC with a particular focus on the recently introduced gemcitabine-free FOLFIRINOX regimen (folinic acid, fluorouracil, irinotecan and oxaliplatin) and nab-paclitaxel + gemcitabine.

Table 2. The evolution of approved therapeutic regimens in patients with metastatic PDAC

	Burris et al. 1997	Moore et al. 2007	Conroy et al. 2011	Von Hoff et al. 2013
Regimen	Gemcitabine vs. 5-FU	Gemcitabine + erlotinib vs. gemcitabine	Gemcitabine vs. FOLFIRINOX	Gemcitabine vs. gemcitabine + nab
Number of patients	126	569	342	861
Population	Advanced PDAC	Advanced PDAC (24.3% LAPC) (~8% prior resection of primary tumour)	Metastatic PDAC	Metastatic PDAC
<i>Characteristics</i>				
Biliary stent	Not mentioned	Not mentioned	15.8%	17%
Head tumors	Not mentioned	Not mentioned	39.2%	43%
ECOG/Karnofsky PS	PS 80–90~30% PS 50–70~70%	ECOG 0–1~80% ECOG 2~20%	ECOG 0–1~99 ECOG 2~1%	PS 90–100~60% PS 60–90~40%
Objective response rate, %	5.4 vs. 0	8.6 vs. 8	9.4 vs. 31.6	7 vs. 23
Disease control rate, %	44.4 vs. 19	57.5 vs. 49.2	50.9 vs. 70.2	33 vs. 48
mPFS/TTP*	9 vs. 4 w*	3.75 vs. 3.55 m	3.3 vs. 6.4 m	3.7 vs. 5.5 m
mOS, m	5.65 vs. 4.41	6.24 vs. 5.91	6.8 vs. 11.1	6.7 vs. 8.5
Survival rates 12 m, %	18 vs. 2	23 vs. 17	20.6 vs. 48.4	22 vs. 35
Treatment effect in subgroup analyses	Not mentioned	PS 2, HR 0.61 Pain-Score <20, HR 0.71 Age <65, HR 0.75	Age >65, HR 0.48 ECOG 1, HR 0.55 Two metastatic sites HR 0.39 No biliary stent HR 0.56	Age <65, HR 0.65 PS 70–80%, HR 0.61 Liver mets HR 0.69 CA 19–9 >59 U/LN, HR 0.61
Specifics	CBR	– More female in the combination arm – Female associated with longer OS	– ‘French-only’ study – ~15% not radiologically evaluable – 38% head tumours	– Only ‘North Americans’ benefited – 42% head tumours

Current Management of Metastatic Disease

From 5-Fluorouracil to Gemcitabine

5-Fluorouracil (5-FU) was considered the only chemotherapeutic option for about 20 years until the introduction of gemcitabine [13, 16–18]. Several clinical studies could show that chemotherapy in advanced pancreatic cancer patients indeed leads to a modest survival benefit as well as improved quality of life (QoL) compared to best supportive care alone [19–21], but the combination of 5-FU with other drugs did not prove to be superior to the single anti-metabolite treatment [16, 22]. During the 1990s, several trials were designed to find new active drugs in pancreatic cancer treatment and the nucleoside analogue gemcitabine (2'-deoxy-2',2'-difluorocytidine) was studied [12, 23]. In 1997, gemcitabine became the first line choice for PDAC patients

due to fewer side effects (compared to 5-FU) and a significant survival benefit (table 2). This clinical study also implemented the concept of clinical benefit response (CBR) that was defined as a $\geq 50\%$ reduction in pain intensity, daily analgesia consumption or ≥ 20 point improvement in Karnofsky performance status (PS) for ≥ 4 consecutive weeks. CBR was significantly improved in gemcitabine-treated patients ($p = 0.0022$) [13]. The CBR was shown to be 23.8% in gemcitabine-treated patients (1,000 mg/m² over 30 min) compared to 4.8% in 5-FU-treated patients (400 mg/m² over 30 min), and the median survival time in the gemcitabine group was 5.65 months compared to 4.41 months in the 5-FU-group, respectively ($p = 0.0025$). In the gemcitabine group, 18% compared to 2% for the 5-FU survived the first 12 months [13]. Several phase III trials with gemcitabine monotherapy revealed a median survival of 5–7 months with a

1-year survival of about 1–25%. Therefore, subsequent chemotherapy trials in PDAC needed to show superiority over standard of care gemcitabine monotherapy. This could be achieved by either of the 2 strategies: (1) combining gemcitabine with a new drug or (2) directly comparing a novel monotherapy or combination therapy against gemcitabine.

Gemcitabine and Fluoropyrimidines

While the results of gemcitabine clearly improved therapeutic efficacy and 1-year survival, its impact on median overall survival (OS) remained at the margin of significance. More intensive combination chemotherapies involving fluoropyrimidines and platinum analogues were investigated in numerous phase II and III trials. Two randomised phase III trials evaluated the combination of gemcitabine and 5-FU compared to gemcitabine alone. In short, the experimental arm did not improve the objective response or median OS [24, 25].

Capecitabine is an oral, tumour-selective fluoropyrimidine carbamate and pro-drug that is activated by a 3-step-targeted process (carboxylesterases, cytidine deaminase and thymidine phosphorylase, respectively). Capecitabine can be used in schedules that provide prolonged fluorouracil exposure at lower peak concentrations, thus mimicking continuous infusion of fluorouracil. Preclinical studies have shown no synergistic effect of capecitabine anti-tumour activity when combined with gemcitabine; however, relevant toxicity was noted in genetically engineered mice of pancreatic cancer more recently [26]. Herrmann and Cunningham published 2 randomised phase III trials of gemcitabine +/- capecitabine (650 or 830 mg/m² twice daily) in patients with metastatic PDAC. There was no statistically significant improvement of the median OS in the combination arm (8.4 vs. 7.2 m and 7.4 vs. 6.0 m; $p = 0.234$ and $p = 0.08$). However, a subgroup of patients with good PS (Karnofsky performance score 90–100) benefited (10.1 vs. 7.4 months, respectively; $p = 0.014$) from the combination treatment. In addition, in the Cunningham et al. [27] study, gemcitabine and capecitabine significantly improved the response rate (RR) (19.1 vs. 12.4%, $p = 0.034$) and progression-free survival (HR 0.78, $p = 0.004$). Interestingly, by pooling the data set of these 2 phase III trials and the phase II trial of Schreithauer in 935 patients, statistical significance could be achieved for median OS (HR 0.86; 95% CI 0.75–0.98, $p = 0.02$) [19, 20, 28]. Independently from this data, Hubner et al. [29] presented single-centre results of the gemcitabine plus capecitabine combination, leading to a median OS of 8.7 m (95% CI 6.7–10.7) and 1-year survival

rate of 34%. Despite the fact that gemcitabine combined with fluoropyrimidine has reliable activity in metastatic PDAC, the QoL did not significantly differ between the 2 treatment arms [29–31]. Based on this data, the combination GEMCAP has replaced 5-FU therapy in clinical practice, especially in the United Kingdom.

Gemcitabine in Combination with

Platinum-Derivates and Topoisomerase Inhibitors

There have been numerous phase II and III studies attempting to improve the efficacy and OS of chemotherapy in metastatic PDAC by using gemcitabine-based combination therapies. The combination of gemcitabine with platinum-derivates was evaluated in 11 trials in more than 2,000 patients [31]. One of the most promising trials was the GERCOR/GISCAD study where the combination of gemcitabine and oxaliplatin improved the PFS (5.58 vs. 3.7 months), CBR (38.2 vs. 26.9%) and RR (26.8 vs. 17.3%). However, no statistical significance was reached for OS [32] and the subsequent phase III trials did not confirm these encouraging results [33–35]. A recently published meta-analysis compared gemcitabine plus oxaliplatin with gemcitabine alone. Here, ORs of 1.33 (95% CI 1.05–1.69, $p = 0.019$) for OS and ORs of 1.38 (95% CI 1.08–1.76, $p = 0.011$) for PFS demonstrated and showed statistical significance [19, 20, 28, 31].

Similar results were obtained for gemcitabine and topoisomerase inhibitors (irinotecan and exatecan) combinations. Although preliminary data suggested a relevant clinical activity for topoisomerase inhibitors, 4 randomised clinical trials revealed no significant improvement of PFS or OS [36–39]. Finally, in the Cancer and Leukemia Group B (CALGB) study, 3 relevant combination therapies (gemcitabine plus cisplatin, gemcitabine plus docetaxel, gemcitabine plus irinotecan) vs. gemcitabine monotherapy demonstrated no relevant 6-month survival benefit for the experimental arms [36]. Therefore, the authors made a decision to refrain from further investigating gemcitabine-based combinations for PDAC.

Gemcitabine and Erlotinib

The epidermal growth factor receptor inhibitor erlotinib was the first drug that was shown to be beneficial in combination with gemcitabine in patients with advanced pancreatic cancer (table 2). In the PA.3 trial, 569 patients were randomised with both locally advanced and metastatic disease to receive gemcitabine or gemcitabine plus erlotinib. Though OS was significantly improved with combination therapy (median survival of 6.2 vs. 5.9

months), clinical relevance of a 2-week survival benefit had to be questioned [40]. This marginal benefit also came at the expense of toxicity with 6 treatment-related deaths reported during the study – all within the combination therapy group. Eight patients from the study (7 from the erlotinib cohort) also developed interstitial lung disease and the risk-benefit of this drug combination remains a controversial topic [41].

Interestingly, the combination of erlotinib and gemcitabine achieved astonishing response in a small subset of patients. It was noted that those patients developing a rash of grade ≥ 2 in severity showed a median survival of 10.5 months and 1-year survival of 43% in contrast with 5.3 months and 16% respectively in patients with no rash. Therefore, the German S3-guideline for exocrine pancreatic cancer recommends an initial therapeutic attempt with erlotinib and gemcitabine for an 8-week period. After this time, treatment should be continued only if a skin rash develops [11]. This interesting finding could be recapitulated in another study by Vaccaro et al. [42]; however, dose-escalation did not yield further therapeutic efficacy.

Folinic Acid, Fluorouracil, Irinotecan and Oxaliplatin (FOLFIRINOX)

Several studies were performed to investigate gemcitabine-based polychemotherapy regimens comprising several cytotoxic drugs. The PEFG protocol compared cisplatin, epirubicin, 5-FU and gemcitabine to gemcitabine alone [43]. The same group introduced another 2, 4-drug combinations based on the PEFG regimen called PEXG (cisplatin, epirubicin, capecitabine and gemcitabine) and PDGX (cisplatin, docetaxel, capecitabine and gemcitabine). Although median OS of 11 m were reached in this phase II study, the results were interpreted with caution, since only 2/3 of the patients had metastatic disease [44]. Another regimen called G-FLIP comprised CPT-11 (irinotecan), gemcitabine, 5-FU, leucovorin and cisplatin [45], and subsequently FOLFOX-6 and FOLFIRI-3 were evaluated in the first-line setting of advanced PDAC [46, 47]. Despite median OS times between 8 and 12 months and higher RRs, increased major toxicities, the inhomogeneity of the patient cohorts and the insufficient inclusion criteria gave rise to doubts whether polychemotherapy was the adequate treatment strategy.

FOLFIRINOX is a chemotherapy regimen comprising 4 drugs – folinic acid, 5-FU, irinotecan and oxaliplatin. This combination of drugs was supported by preclinical studies demonstrating either single agent efficacy against pancreatic cancer or synergistic activity in combination

with a fellow agent. Based on ambitious phase I/II data in which FOLFIRINOX revealed a good safety profile and appealing RRs, Conroy et al. [48] conducted a French phase II/III trial (PRODIGE) with OS as primary objective, and PFS, QoL, RR and toxicity as secondary endpoints [48, 49]. In total, 342 patients were enrolled and FOLFIRINOX was administered with the following dose: oxaliplatin at a dose of 85 mg/m² over 2 h followed by leucovorin at a dose of 400 mg/m² given as a 2-hour intravenous infusion and irinotecan at a dose of 180 mg/m² in a 90-minute intravenous infusion [50]. This treatment was immediately followed by 5-FU at a dose of 400 mg/m², administered by intravenous bolus, followed by a continuous intravenous infusion of 2,400 mg/m² over a 46-hour period every 2 weeks. The patients on FOLFIRINOX demonstrated a median survival of 11.1 months, which was clearly superior when compared to the 6.8 months of the gemcitabine control group (table 2). The median progression-free survival was 6.4 months in FOLFIRINOX-treated patients versus 3.3 months in patients who received gemcitabine [50]. Compared to treatment with gemcitabine, treatment with FOLFIRINOX resulted in a superior tumour RR (9.4 vs. 31.6%); however, 50 patients (25 per arm) were not radiologically assessable. Yet in 2005, this regime showed promising results, when it had been administered to a heterogeneous group of patients just defined as histologically proven advanced PDAC, but containing both LAPC and metastatic PDAC. Thus, the treatment regimen was not exclusively restricted to patients suffering from metastatic disease [48]. However, in order to achieve the benefits shown, the FOLFIRINOX regimen requires a careful selection of patients, which implicates strict limitations as the potential real-life first line option. In the study by Conroy et al., only patients with nearly unrestricted ECOG-PS of 0–1, below 76 years of age, no cardiac ischemia within 1 year before entry, and total bilirubin levels below 1.5 times the upper normal limit were included. Interestingly, only 35–40% suffered from a pancreatic head adenocarcinoma and therefore, solely 15% received stenting of the biliary duct. No single cholangitis had been observed during the course of the trial. This difference may be related to the exclusion of patients with elevated bilirubin levels, because of the increased risk of irinotecan-induced toxicity [51]. As shown by Conroy et al., even de-escalation (n = 80 received second-line treatment in the FOLFIRINOX arm) might be necessary; yet it resulted in an impressive median OS of 4.4 months from the beginning of second-line chemotherapy. Particularly, this accounts as one explanation for the 1-year survival rate of 48.4% for patients

treated with FOLFIRINOX versus 20.6% for patients receiving gemcitabine ($p < 0.001$). Despite the strict selection criteria for the study, patients on FOLFIRINOX suffered more frequently from adverse events or severe side effects compared to the patients on gemcitabine. Forty five percent of the FOLFIRINOX patients developed neutropenia and 5.4% showed febrile neutropenia. In addition, thrombocytopenia (9.1%), diarrhea (12.7%) and sensory neuropathy (9.0%) occurred significantly more often in FOLFIRINOX patients, which implies a need for increased clinical routine check-up intervals for patients receiving this intensive regime. Moreover, supportive therapies such as nutritional support, G-CSF treatment or antibiotics are more often needed, and the discontinuation of the therapy may be required. However, G-CSF was not recommended in this trial to prevent neutropenia. Two years after the publication of the primary study data, QoL evaluations were presented [52]. Although FOLFIRINOX had remarkable side effects, it significantly reduced QoL impairment compared with gemcitabine in patients with metastatic PDAC. Only diarrhea was significantly increased in the FOLFIRINOX arm. Beyond the PS, age >65 years and low serum albumin were seen as independent prognostic factors for poor survival in this situation.

Gemcitabine and Nab-Paclitaxel

In 2013, a second intensified combination-chemotherapy regimen – gemcitabine with nab-paclitaxel – was presented for the treatment of patients suffering from metastatic PDAC Metastatic Pancreatic Adenocarcinoma Trial (MPACT-Trial).

Nab-paclitaxel is a nanoparticle-sized, albumin-bound paclitaxel, which was originally developed to avoid toxic and immunogenic solvents of hydrophobic paclitaxel, and was first approved by the FDA in breast cancer patients in 2005 [7, 53–57].

In PDAC, Von Hoff et al. [53, 54] demonstrated in a phase II trial that patients with SPARC (secreted protein acidic and rich in cysteine) positive tumours revealed a highly significant benefit in OS when treated with gemcitabine plus nab-paclitaxel. Therefore, it was hypothesised that stromal SPARC as an albumin-binding protein would bind albumin-coated paclitaxel molecules, thereby selectively increasing drug delivery. However, preclinical data with genetically ablated SPARC mice showed comparable nab-paclitaxel concentrations within the endogenous murine pancreatic tumours compared to neoplasms overexpressing SPARC [58]. Controversial data in men and mice exist regarding the potential of nab-pacli-

taxel to deplete abundant tumour stroma in PDAC [55, 59, 60]. Therefore, it remains questionable whether nab-paclitaxel exerts any tumour-selective/targeted effect beyond its cytotoxicity as a mitotic inhibitor.

Nevertheless, the international multi-centre MPACT-trial revealed significant clinical benefits, achieving disease control rates of 67% in treated patients and a median OS of 8.5 months [53, 54, 61] (table 2).

MPACT trial patients ($n = 431$) receiving the combination treatment of gemcitabine plus nab-paclitaxel showed a 1-year survival rate of 35 vs. 22% when compared to the gemcitabine monotherapy group ($n = 430$), and 9% compared to 4% at the second year of follow-up. Moreover, a median progression-free survival of 5.5 months in the combination therapy cohort versus 3.7 months in the gemcitabine monotherapy group had been achieved. Severe neutropenia was significantly more frequent in the combination therapy group of the MPACT trial (gemcitabine + nab-paclitaxel: 38%, gemcitabine: 27%), while febrile neutropenia occurred in 3% of the patients. The same was true for the incidence of fatigue (17 vs. 7%) and neuropathy (17 vs. 1%) that occurred significantly more often in the nab-paclitaxel group than in the gemcitabine monotherapy group [53].

Strikingly, immunohistochemical analysis from MPACT phase III patients failed to confirm that SPARC is a prognostic biomarker [62], confirming the earlier published preclinical data [58].

In a recently published phase-III-trial ($n = 861$ patients) by Goldstein et al. [63], analysing the long-term-survival of patients receiving the nab-paclitaxel plus gemcitabine combination-treatment, the superior OS and PFS could be confirmed. Moreover, subgroup analysis emphasised the relevance of CA 19–9 and neutrophil to lymphocyte ratio as reasonable prognostic markers. High CA 19–9 levels and neutrophil to lymphocyte ratio before treatment was associated with a worse OS. Survivors of more than 3 years were exclusively identified in the nab-paclitaxel plus gemcitabine arm (4%) [63]. By performing post-hoc analyses of the MPACT collective, Tabernero et al. [64] described PS score, liver metastases, age and number of metastatic sites as consistent and valid predictors of survival that are easily available clinical markers that help in decision making regarding treatment.

Notably, a retrospective analysis showed that the eligibility criteria itself for both the PRODIGE and MPACT trial, were associated with an improved survival [65]. The authors demonstrated that patients who simply fulfilled the inclusion criteria for either FOLFIRINOX or nab-paclitaxel/gemcitabine, without actually receiving the treat-

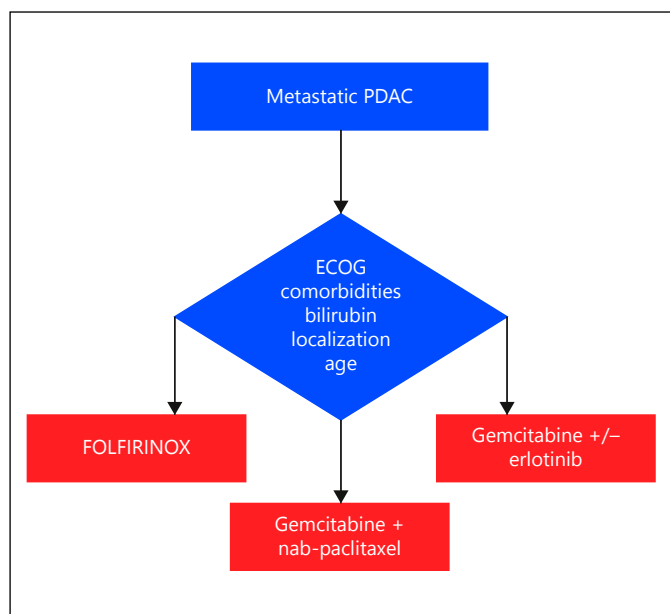


Fig. 1. Decision-making algorithm in patients with metastatic PDAC.

ments, had a better median OS compared to patients who failed to meet them. When comparing the FOLFIRINOX-eligible population with the nab-paclitaxel-eligible group, it becomes apparent that ECOG 2 patients were excluded in the FOLFIRINOX trial. These results were consistent with the fact that eligibility was no longer a significant prognostic factor after accounting for patient's ECOG performance. Strictly following the trials inclusion criteria, the authors demonstrated that the majority of patients with metastatic PDAC were not eligible for either of the intensified polychemotherapeutic regimens. Comparing only eligibility for treatment for nab-paclitaxel plus gemcitabine versus the FOLFIRINOX protocol, nearly twice as many patients could have been candidates for nab-paclitaxel due to less restrictive ECOG performance criteria for this regimen in trials [65].

Furthermore, novel drug formulations that improve the pharmacokinetic properties of hydrophobic paclitaxel have been investigated. For instance, L  hr et al. [66] have shown in a phase II trial that paclitaxel embedded in cationic liposomes, the so-called EndoTAG-1, was generally well tolerated and achieved a median OS of 8.1–9.3 months when combined with gemcitabine.

Ongoing clinical trials are investigating nab-paclitaxel as the backbone for novel targeted therapies. Examples are ruxolitinib, a janus-kinase inhibitor in combination with gemcitabine or nab-paclitaxel plus gemcitabine

(NCT01822756), INCB039110 a JAK1 inhibitor in combination with nab-paclitaxel plus gemcitabine (NCT01858883), or the indoleamine-2,3-dioxygenase inhibitor Indoximod in combination with nab-paclitaxel plus gemcitabine in advanced PDAC (NCT02077881). Those results might help to optimise the selection of adequate patient cohorts eligible for nab-paclitaxel, and moreover provide additional insights into novel targeted treatment avenues (table 1).

Conclusion

It is evident from the existing data that there is a significant survival benefit of intensive chemotherapy treatment regimens FOLFIRINOX and gemcitabine + nab-paclitaxel for metastatic PDAC. Although OS rates may be overestimated due to very stringent enrolment criteria for these trials, national and international guidelines recommend them as first-line therapy for metastatic PDAC. However, careful patient selection based on clinical and laboratory findings represents a major challenge for physicians and oncologists in the palliative situation (fig. 1). Currently, no biomarker can reliably predict the response to treatment to nab-paclitaxel + gemcitabine or FOLFIRINOX. Therefore, a careful clinical and biochemical follow-up is required to optimise the treatment effects while minimising the side effects. Often, dose reductions are a feasible approach to cope with the enhanced toxicity profile of these protocols. For the future, intensified chemotherapies such as nab-paclitaxel and FOLFIRINOX may also be extended to selected patients with LAPC in a neoadjuvant setting, as well as for adjuvant treatment strategies. Furthermore, intensified chemotherapy protocols are currently investigated as backbone for novel investigational PDAC therapies, such as anti-stromal approaches or immune cell checkpoint antagonists.

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References

- Siegel RL, Miller KD, Jemal A: Cancer statistics, 2015. *CA Cancer J Clin* 2015;65:5–29.
- Ryan DP, Hong TS, Bardeesy N: Pancreatic adenocarcinoma. *N Engl J Med* 2014;371:2140–2141.
- Löhr M, Klöppel G, Maisonneuve P, Lowenfels AB, Lüttges J: Frequency of K-ras mutations in pancreatic intraductal neoplasias associated with pancreatic ductal adenocarcinoma and chronic pancreatitis: a meta-analysis. *Neoplasia* 2005;7:17–23.
- Almoguera C, Shibata D, Forrester K, Martin J, Arnheim N, Perucho M: Most human carcinomas of the exocrine pancreas contain mutant c-K-ras genes. *Cell* 1988;53:549–554.
- Hezel AF, Kimmelman AC, Stanger BZ, Bardeesy N, Depinho RA: Genetics and biology of pancreatic ductal adenocarcinoma. *Genes Dev* 2006;20:1218–1249.
- Feig C, Gopinathan A, Neesse A, Chan DS, Cook N, Tuveson DA: The pancreas cancer microenvironment. *Clin Cancer Res* 2012;18:4266–4276.
- Neesse A, Michl P, Frese KK, Feig C, Cook N, Jacobetz MA, Lolkema MP, Buchholz M, Olive KP, Gress TM, Tuveson DA: Stromal biology and therapy in pancreatic cancer. *Gut* 2011;60:861–868.
- Neesse A, Algül H, Tuveson DA, Gress TM: Stromal biology and therapy in pancreatic cancer: a changing paradigm. *Gut* 2015;64:1476–1484.
- Modolell I, Guarner L, Malagelada JR: Varieties of clinical presentation of pancreatic and biliary tract cancer. *Ann Oncol* 1999;10(suppl 4):82–84.
- Porta M, Fabregat X, Malats N, Guarner L, Carrato A, de Miguel A, Ruiz L, Jariod M, Costafreda S, Coll S, Alguacil J, Corominas JM, Solà R, Salas A, Real FX: Exocrine pancreatic cancer: symptoms at presentation and their relation to tumour site and stage. *Clin Transl Oncol* 2005;7:189–197.
- Seufferlein T, Porzner M, Becker T, Budach V, Ceyhan G, Esposito I, Fietkau R, Follmann M, Friess H, Galle P, Geissler M, Glanemann M, Gress T, Heinemann V, Hohenberger W, Hopt U, Izbicki J, Klar E, Kleeff J, Kopp I, Kullmann F, Langer T, Langrehr J, Lerch M, Löhr M, Lüttges J, Lutz M, Mayerle J, Michl P, Möller P, Molls M, Münter M, Nothacker M, Oettle H, Post S, Reinacher-Schick A, Röcken C, Roeb E, Saeger H, Schmid R, Schmiegel W, Schoenberg M, Siveke J, Stuschke M, Tannapfel A, Uhl W, Unverzagt S, van Oorschot B, Vashist Y, Werner J, Yekbas E; Guidelines Programme Oncology AWMF; German Cancer Society eV; German Cancer Aid: [S3-guideline exocrine pancreatic cancer]. *Z Gastroenterol* 2013;51:1395–1440.
- Rothenberg ML, Moore MJ, Cripps MC, Andersen JS, Portenoy RK, Burris HA 3rd, Green MR, Tarassoff PG, Brown TD, Casper ES, Storniolo AM, Von Hoff DD: A phase II trial of gemcitabine in patients with 5-FU-refractory pancreas cancer. *Ann Oncol* 1996;7:347–353.
- Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD: Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997;15:2403–2413.
- Löhr M: Is it possible to survive pancreatic cancer? *Nat Clin Pract Gastroenterol Hepatol* 2006;3:236–237.
- Löhr JM: Medical treatment of pancreatic cancer. *Expert Rev Anticancer Ther* 2007;7:533–544.
- Ducreux M, Rougier P, Pignon JP, Douillard JY, Seitz JF, Bugat R, Bosset JF, Merouche Y, Raoul JL, Ychou M, Adenis A, Berthault-Cvitkovic F, Lubinski M; Groupe Digestif de la Fédération Nationale des Centres de Lutte Contre le Cancer Digestif: A randomised trial comparing 5-FU with 5-FU plus cisplatin in advanced pancreatic carcinoma. *Ann Oncol* 2002;13:1185–1191.
- Moertel CG, Frytak S, Hahn RG, O'Connell MJ, Reitemeier RJ, Rubin J, Schutt AJ, Weiland LH, Childs DS, Holbrook MA, Lavin PT, Livstone E, Spiro H, Knowlton A, Kalsner M, Barkin J, Lessner H, Mann-Kaplan R, Ramming K, Douglas HO Jr, Thomas P, Nave H, Bateman J, Lokich J, Brooks J, Chaffey J, Corson JM, Zameck N, Novak JW: Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: the gastrointestinal tumor study group. *Cancer* 1981;48:1705–1710.
- Moertel CG, Douglas HO Jr, Hanley J, Carbone PP: Treatment of advanced adenocarcinoma of the pancreas with combinations of streptozotocin plus 5-fluorouracil and streptozotocin plus cyclophosphamide. *Cancer* 1977;40:605–608.
- Sultana A, Tudur Smith C, Cunningham D, Starling N, Tait D, Neoptolemos JP, Ghaneh P: Systematic review, including meta-analyses, on the management of locally advanced pancreatic cancer using radiation/combined modality therapy. *Br J Cancer* 2007;96:1183–1190.
- Sultana A, Smith CT, Cunningham D, Starling N, Neoptolemos JP, Ghaneh P: Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. *J Clin Oncol* 2007;25:2607–2615.
- Yip D, Karapetis C, Strickland A, Steer CB, Goldstein D: Chemotherapy and radiotherapy for inoperable advanced pancreatic cancer. *Cochrane Database Syst Rev* 2006;3:CD002093.
- Ducreux M, Mitry E, Ould-Kaci M, Boige V, Seitz JF, Bugat R, Breau JL, Bouché O, Etienne PL, Tigaud JM, Morvan F, Cvitkovic E, Rougier P: Randomized phase II study evaluating oxaliplatin alone, oxaliplatin combined with infusional 5-FU, and infusional 5-FU alone in advanced pancreatic carcinoma patients. *Ann Oncol* 2004;15:467–473.
- Rothenberg ML: New developments in chemotherapy for patients with advanced pancreatic cancer. *Oncology (Williston Park)* 1996;10(9 suppl):18–22.
- Berlin JD, Catalano P, Thomas JP, Kugler JW, Haller DG, Benson AB 3rd: Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: eastern cooperative oncology group trial E2297. *J Clin Oncol* 2002;20:3270–3275.
- Di Costanzo F, Carlini P, Doni L, Massidda B, Mattioli R, Iop A, Barletta E, Moscetti L, Recchia F, Tralongo P, Gasperoni S: Gemcitabine with or without continuous infusion 5-FU in advanced pancreatic cancer: a randomised phase II trial of the Italian oncology group for clinical research (GOIRC). *Br J Cancer* 2005;93:185–189.
- Courtin A, Richards FM, Bapiro TE, Bramhall JL, Neesse A, Cook N, Krippendorff BF, Tuveson DA, Jodrell DI: Anti-tumour efficacy of capecitabine in a genetically engineered mouse model of pancreatic cancer. *PLoS One* 2013;8:e67330.
- Cunningham D, Chau I, Stocken DD, Valle JW, Smith D, Steward W, Harper PG, Dunn J, Tudur-Smith C, West J, Falk S, Crellin A, Adab F, Thompson J, Leonard P, Ostrowski J, Eatock M, Scheithauer W, Herrmann R, Neoptolemos JP: Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol* 2009;27:5513–5518.
- Heinemann V, Boeck S, Hinke A, Labianca R, Louvet C: Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. *BMC Cancer* 2008;8:82.
- Hubner RA, Worsnop F, Cunningham D, Chau I: Gemcitabine plus capecitabine in unselected patients with advanced pancreatic cancer. *Pancreas* 2013;42:511–515.
- Bernhard J, Dietrich D, Scheithauer W, Gerber D, Bodoky G, Ruhstaller T, Glimelius B, Bajetta E, Schüller J, Saletti P, Bauer J, Figer A, Pestalozzi BC, Köhne CH, Mingrone W, Stemmer SM, Tamas K, Kornek GV, Koeberle D, Herrmann R; Central European Cooperative Oncology Group: Clinical benefit and quality of life in patients with advanced pancreatic cancer receiving gemcitabine plus capecitabine versus gemcitabine alone: a randomized multicenter phase III clinical trial – SAKK 44/00-CECOG/PAN.1.3.001. *J Clin Oncol* 2008;26:3695–3701.

- 31 Hu J, Zhao G, Wang HX, Tang L, Xu YC, Ma Y, Zhang FC: A meta-analysis of gemcitabine containing chemotherapy for locally advanced and metastatic pancreatic adenocarcinoma. *J Hematol Oncol* 2011;4:11.
- 32 Louvet C, Labianca R, Hammel P, Lledo G, Zampino MG, André T, Zaniboni A, Ducreux M, Aitini E, Taïeb J, Faroux R, Lepere C, de Gramont A; GERCOR; GISCAD: Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol* 2005;23:3509–3516.
- 33 Poplin E, Feng Y, Berlin J, Rothenberg ML, Hochster H, Mitchell E, Alberts S, O'Dwyer P, Haller D, Catalano P, Cella D, Benson AB 3rd: Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the eastern cooperative oncology group. *J Clin Oncol* 2009;27:3778–3785.
- 34 Heinemann V, Quietzsch D, Gieseler F, Gonnemann M, Schöneke H, Rost A, Neuhaus H, Haag C, Clemens M, Heinrich B, Vehlting-Kaiser U, Fuchs M, Fleckenstein D, Gesierich W, Uthgenannt D, Einsele H, Holstege A, Hinke A, Schalhorn A, Wilkowski R: Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol* 2006;24:3946–3952.
- 35 Colucci G, Giuliani F, Gebbia V, Biglietto M, Rabitti P, Uomo G, Cigolari S, Testa A, Maiello E, Lopez M: Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma: a prospective, randomized phase III study of the gruppo oncologia dell'italia meridionale. *Cancer* 2002;94:902–910.
- 36 Kulke MH, Tempero MA, Niedzwiecki D, Hollis DR, Kindler HL, Cusnir M, Enzinger PC, Gorsch SM, Goldberg RM, Mayer RJ: Randomized phase II study of gemcitabine administered at a fixed dose rate or in combination with cisplatin, docetaxel, or irinotecan in patients with metastatic pancreatic cancer: CALGB 89904. *J Clin Oncol* 2009;27:5506–5512.
- 37 Abou-Alfa GK, Letourneau R, Harker G, Modiano M, Hurwitz H, Tchekmedyan NS, Feit K, Ackerman J, De Jager RL, Eckhardt SG, O'Reilly EM: Randomized phase III study of exatecan and gemcitabine compared with gemcitabine alone in untreated advanced pancreatic cancer. *J Clin Oncol* 2006;24:4441–4447.
- 38 Stathopoulos GP, Syrigos K, Aravantinos G, Polyzos A, Papakotoulas P, Fountzilias G, Potamianou A, Ziras N, Boukovinas J, Varthalitis J, Androulakis N, Kotsakis A, Samonis G, Georgoulas V: A multicenter phase III trial comparing irinotecan-gemcitabine (IG) with gemcitabine (G) monotherapy as first-line treatment in patients with locally advanced or metastatic pancreatic cancer. *Br J Cancer* 2006;95:587–592.
- 39 Rocha Lima CM, Green MR, Rotche R, Miller WH Jr, Jeffrey GM, Cisar LA, Morganti A, Orlando N, Gruia G, Miller LL: Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol* 2004;22:3776–3783.
- 40 Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, Campos D, Lim R, Ding K, Clark G, Voskoglou-Nomikos T, Ptasynski M, Parulekar W; National Cancer Institute of Canada Clinical Trials Group: Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the national cancer institute of canada clinical trials group. *J Clin Oncol* 2007;25:1960–1966.
- 41 Péron J, Roy P, Ding K, Parulekar WR, Roche L, Buyse M: Assessing the benefit-risk of new treatments using generalised pairwise comparisons: the case of erlotinib in pancreatic cancer. *Br J Cancer* 2015;112:971–976.
- 42 Vaccaro V, Bria E, Sperduti I, Gelibter A, Moschetti L, Mansueto G, Ruggeri EM, Gamucci T, Cognetti F, Milella M: First-line erlotinib and fixed dose-rate gemcitabine for advanced pancreatic cancer. *World J Gastroenterol* 2013;19:4511–4519.
- 43 Reni M, Cordio S, Milandri C, Passoni P, Bonetto E, Oliani C, Luppi G, Nicoletti R, Galli L, Bordonaro R, Passardi A, Zerbi A, Balzano G, Aldrighetti L, Staudacher C, Villa E, Di Carlo V: Gemcitabine versus cisplatin, epirubicin, fluorouracil, and gemcitabine in advanced pancreatic cancer: a randomised controlled multicentre phase III trial. *Lancet Oncol* 2005;6:369–376.
- 44 Reni M, Cereda S, Rognone A, Belli C, Ghidini M, Longoni S, Fugazza C, Rezzonico S, Passoni P, Slim N, Balzano G, Nicoletti R, Cappio S, Doglioni C, Villa E: A randomized phase II trial of two different 4-drug combinations in advanced pancreatic adenocarcinoma: cisplatin, capecitabine, gemcitabine plus either epirubicin or docetaxel (PEXG or PDXG regimen). *Cancer Chemother Pharmacol* 2012;69:115–123.
- 45 Goel A, Grossbard ML, Malamud S, Homel P, Dietrich M, Rodriguez T, Mirzoyev T, Kozuch P: Pooled efficacy analysis from a phase I-II study of biweekly irinotecan in combination with gemcitabine, 5-fluorouracil, leucovorin and cisplatin in patients with metastatic pancreatic cancer. *Anticancer Drugs* 2007;18:263–271.
- 46 Ghosn M, Farhat F, Kattan J, Younes F, Moukadem W, Nasr F, Chahine G: FOLFOX-6 combination as the first-line treatment of locally advanced and/or metastatic pancreatic cancer. *Am J Clin Oncol* 2007;30:15–20.
- 47 Taïeb J, Lecomte T, Aparicio T, Asnacios A, Mansoubakht T, Artru P, Fallik D, Spano JP, Landi B, Lledo G, Desrame J: FOLFIRI.3, a new regimen combining 5-fluorouracil, folinic acid and irinotecan, for advanced pancreatic cancer: results of an association des gastro-entérologues oncologues (gastroenterologist oncologist association) multicenter phase II study. *Ann Oncol* 2007;18:498–503.
- 48 Conroy T, Paillot B, François E, Bugat R, Jacob JH, Stein U, Nasca S, Metges JP, Rixe O, Michel P, Magherini E, Hua A, Deplanque G: Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer – a groupe tumeurs digestives of the federation nationale des centres de lutte contre le cancer study. *J Clin Oncol* 2005;23:1228–1236.
- 49 Ychou M, Conroy T, Seitz JF, Gourgou S, Hua A, Mery-Mignard D, Kramar A: An open phase I study assessing the feasibility of the triple combination: oxaliplatin plus irinotecan plus leucovorin/ 5-fluorouracil every 2 weeks in patients with advanced solid tumors. *Ann Oncol* 2003;14:481–489.
- 50 Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bannoun J, Bachet JB, Khemissa-Akoud F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M; Groupe Tumeurs Digestives of Unicancer; PRODIGE Inter-group: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817–1825.
- 51 Ueno H, Okusaka T, Funakoshi A, Ishii H, Yamao K, Ishikawa O, Ohkawa S, Saitoh S: A phase II study of weekly irinotecan as first-line therapy for patients with metastatic pancreatic cancer. *Cancer Chemother Pharmacol* 2007;59:447–454.
- 52 Gourgou-Bourgade S, Bascoul-Molle C, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Boige V, Bérille J, Conroy T: Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. *J Clin Oncol* 2013;31:23–29.
- 53 Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandini SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF: Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013;369:1691–1703.
- 54 Von Hoff DD, Ramanathan RK, Borad MJ, Laheru DA, Smith LS, Wood TE, Korn RL, Desai N, Trieu V, Iglesias JL, Zhang H, Soon-Shiong P, Shi T, Rajeshkumar NV, Maitra A, Hidalgo M: Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. *J Clin Oncol* 2011;29:4548–4554.

- 55 Frese KK, Neesse A, Cook N, Bapiro TE, Lolkema MP, Jodrell DI, Tuveson DA: Nab-paclitaxel potentiates gemcitabine activity by reducing cytidine deaminase levels in a mouse model of pancreatic cancer. *Cancer Discov* 2012;2:260–269.
- 56 Infante JR, Jones SF, Bendell JC, Spigel DR, Yardley DA, Weekes CD, Messersmith WA, Hainsworth JD, Burris HA 3rd: A phase I, dose-escalation study of pomalidomide (CC-4047) in combination with gemcitabine in metastatic pancreas cancer. *Eur J Cancer* 2011;47:199–205.
- 57 Gradishar WJ, Tjulandin S, Davidson N, Shaw H, Desai N, Bhar P, Hawkins M, O'Shaughnessy J: Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer. *J Clin Oncol* 2005;23:7794–7803.
- 58 Neesse A, Frese KK, Chan DS, Bapiro TE, Howat WJ, Richards FM, Ellenrieder V, Jodrell DI, Tuveson DA: SPARC independent drug delivery and antitumour effects of nab-paclitaxel in genetically engineered mice. *Gut* 2014;63:974–983.
- 59 Alvarez R, Musteanu M, Garcia-Garcia E, Lopez-Casas PP, Megias D, Guerra C, Muñoz M, Quijano Y, Cubillo A, Rodriguez-Pascual J, Plaza C, de Vicente E, Prados S, Tabernero S, Barbacid M, Lopez-Rios F, Hidalgo M: Stromal disrupting effects of nab-paclitaxel in pancreatic cancer. *Br J Cancer* 2013;109:926–933.
- 60 Neesse A, Michl P, Tuveson DA, Ellenrieder V: Nab-paclitaxel: novel clinical and experimental evidence in pancreatic cancer. *Z Gastroenterol* 2014;52:360–366.
- 61 Von Hoff DD, Ramanathan R, Borad M, Laheru D, Smith L, Wood T, Korn R, Desai N, Iglesias J, Hidalgo M: SPARC correlation with response to gemcitabine (G) plus nab-paclitaxel (nab-P) in patients with advanced metastatic pancreatic cancer: a phase I/II study. *J Clin Oncol* 2009;27:4525.
- 62 Hidalgo M, Plaza C, Illei P, et al: SPARC Analysis in the Phase III MPACT Trial of Nab-Paclitaxel (nab-p) Plus Gemcitabine (gem) vs Gem Alone for Patients with Metastatic Pancreatic Cancer. Barcelona, 16th World Congress on Gastrointestinal Cancer, 2014.
- 63 Goldstein D, El-Maraghi RH, Hammel P, Heinemann V, Kunzmann V, Sastre J, Scheithauer W, Siena S, Tabernero J, Teixeira L, Tortora G, Van Laethem JL, Young R, Penenberg DN, Lu B, Romano A, Von Hoff DD: Nab-paclitaxel plus gemcitabine for metastatic pancreatic cancer: long-term survival from a phase III trial. *J Natl Cancer Inst* 2015; 107:pii.
- 64 Tabernero J, Chiorean EG, Infante JR, Hingorani SR, Ganju V, Weekes C, Scheithauer W, Ramanathan RK, Goldstein D, Penenberg DN, Romano A, Ferrara S, Von Hoff DD: Prognostic factors of survival in a randomized phase III trial (MPACT) of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic pancreatic cancer. *Oncologist* 2015;20:143–150.
- 65 Peixoto RD, Ho M, Renouf DJ, Lim HJ, Gill S, Ruan JY, Cheung WY: Eligibility of metastatic pancreatic cancer patients for first-line palliative intent nab-paclitaxel plus gemcitabine versus FOLFIRINOX. *Am J Clin Oncol* 2015, Epub ahead of print.
- 66 Lohr JM, Haas SL, Bechstein WO, Bodoky G, Cwiertka K, Fischbach W, Fölsch UR, Jäger D, Osinsky D, Prausova J, Schmidt WE, Lutz MP; CT4001 Study Group: Cationic liposomal paclitaxel plus gemcitabine or gemcitabine alone in patients with advanced pancreatic cancer: a randomized controlled phase II trial. *Ann Oncol* 2012;23:1214–1222.

Appendix SKORUPAN01

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First-Line Treatment of Metastatic Pancreatic Ductal Adenocarcinoma: Did 2024 Offer New Insights?

January 22, 2025

Nebojsa Skorupan, MD, and Christine Alewine, MD, PhD



Key Points:

- The NAPOLI-3 trial established superiority of NALIRIFOX over gemcitabine/nab-paclitaxel (GnP) for first-line treatment of unselected patients with metastatic pancreatic ductal adenocarcinoma (mPDAC).
- NALIRIFOX treatment is more costly than FOLFIRINOX and the relative efficacy of NALIRIFOX versus FOLFIRINOX or modified FOLFIRINOX (mFFX) has yet to be explored head-to-head in a prospective randomized trial.
- Superiority of NALIRIFOX in NAPOLI-3 could be driven by molecular differences in the study population, as compared with the PASS-01 and GENERATE trials; the field awaits publication of outcome data for the DNA damage repair (DDR) wild-type subgroup.



Dr. Nebojsa Skorupan

FOLFIRINOX and GnP chemotherapy have both been demonstrated to improve median overall survival (mOS) compared with single-agent gemcitabine in fit patients with mPDAC when given in the first-line setting.^{1,2} However, in the decade since their initial approvals, no prospective randomized, head-to-head comparisons between the 2 regimens have been conducted. This has left oncologists struggling to choose between them based on toxicity profile alone, given the absence of high-level data on superiority.

For patients with PDAC with tumors containing mutations in DDR-related genes, such as *BRCA1/2* and *PALB2*, excellent data exist that demonstrate that the use of platinum-containing regimens such as FOLFIRINOX in the first-line setting result in improved OS.³⁻⁶ Last year, data from 3 new studies shed light on comparative activity of first-line combination chemotherapy regimens in the remaining mPDAC population.

NAPOLI-3 Sets the Stage

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Explore the data

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Dr. Christine Alewine

Definitive evidence for a superior first-line combination chemotherapy regimen for fit patients with mPDAC is and remains an important milestone in the field. NAPOLI-3, the first prospective randomized phase 3 study to address this issue, compared NALIRIFOX to GnP in the first-line setting in unselected patients with mPDAC and established the superiority of NALIRIFOX.⁷

Although some patients and oncologists might still favor GnP for its lower gastrointestinal toxicities, such as diarrhea, nausea, and vomiting, NALIRIFOX offered approximately 2 months' improvement in mOS, decreased hematologic toxicity, and half the rate of peripheral neuropathy as GnP. The U.S. Food and Drug Administration approved NALIRIFOX for first-line mPDAC treatment in February 2024 based on these data, putting GnP in the backseat in the first-line setting.⁸

However, NAPOLI-3 did not address whether NALIRIFOX represents an improvement over FOLFIRINOX or is simply an equivalent derivative. NALIRIFOX contains the same chemotherapy agents as FOLFIRINOX, except that standard irinotecan is replaced by the more costly nanoliposomal irinotecan (nal-IRI). Although studies exist to support that nal-IRI has a prolonged half-life and achieves improved intratumoral drug concentration compared with standard irinotecan, the efficacy of nal-IRI versus irinotecan has not been directly compared in a prospective randomized clinical trial either alone or in parallel combinations such as NALIRIFOX versus FOLFIRINOX. Although cross-trial comparisons are fraught with issues, NAPOLI-3 and the 2011 PRODIGE-4 study that established FOLFIRINOX as a standard of care had identical 11.1 months mOS, and the 2 studies enrolled a similar patient population.^{1,7} Currently, we lack clear evidence to assess whether the higher cost of NALIRIFOX is compensated by increased efficacy.

Less attention has been paid to 2 other differences between FOLFIRINOX and NALIRIFOX. First, NALIRIFOX eliminates the 5-fluorouracil bolus, mimicking the mFFX adjuvant regimen that improves survival in patients with resectable disease.⁹ This significantly lessens regimen toxicity. Second, NALIRIFOX uses a reduced dose of oxaliplatin as compared with FOLFIRINOX and mFFX, which certainly contributed to the reduction in peripheral neuropathy (3% vs 9%) reported for NALIRIFOX-treated patients in NAPOLI-3 versus FOLFIRINOX-treated patients in PRODIGE-4. These regimen modifications have made NALIRIFOX more tolerable for patients.

PASS-01 and GENERATE Throw a Curveball

Results from the randomized multicenter PASS-01 and GENERATE (JCOG1611) studies, which evaluated the efficacy of first-line mPDAC regimens, were reported at the 2024 ASCO Annual Meeting and 2024 European Society for Medical Oncology Congress. In PASS-01, the still-maturing data show that GnP is superior to mFFX; similarly, the GENERATE study, which was designed to establish the superiority of mFFX (and S-1, irinotecan, and oxaliplatin) over GnP, closed early for futility.^{10,11}

Most likely, differences in study population contributed to the disparate efficacy results of PASS-01 and GENERATE as compared with NAPOLI-3. GENERATE recruited an exclusively Japanese population, a group that has well-known differences in ability to metabolize mFFX components, whereas only 5% of patients in NAPOLI-3 were Asian. Importantly, PASS-01 excluded patients with DDR mutations. Case control studies have estimated a 37% increase in response rate and at least a 13-month increase in OS for patients with a *gBRCA1/2* mutation versus patients with wild-type advanced PDAC who receive platinum-containing regimens.^{5,12} Incidence of DDR mutations in the NAPOLI-3 population has not yet been reported, so it is not possible to